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Express Mail No.: EK916750942US  
Docket No.: 787CIP2C

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
PATENT APPLICATION TRANSMITTAL UNDER 37 CFR 1.53



BOX PATENT APPLICATION  
Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of

Inventor(s): Y. Tom Tang, Chenghua Liu, Vinod Asundi, Ping Zhou, Jie Zhang, Feiyan Ren,  
Qing A. Zhao, Aidong J. Xue, Tom Wehrman, Jian-Rui Wang, Radoje T. Drmanac

Title: NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

1. Type of application

- ☒ This is a new application for a
- ☒ Utility patent.
- ☐ Design patent.
- ☒ This is a continuation-in-part application of prior application no. 09/560,875 filed April 27, 2000, Attorney Docket No. 787CIP, which is a continuation-in-part application of prior application no. 09/496,914 filed February 03, 2000, Attorney Docket No. 787.

2. Application Papers Enclosed

- 1 Title Page
- 121 Pages of Specification (excluding Claims, Abstract, Drawings & Sequence Listing)
- 4 Page(s) of Claims
- 1 Page(s) of Abstract
- 0 Sheet(s) of Drawings (Figs. X-X) ☐ Formal ☐ Informal
- 575 Page(s) of Sequence Listing

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Patent Application Transmittal and the documents referred to as enclosed therewith are being deposited with the United States Postal Service on **September 01, 2000**, in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 utilizing the "Express Mail Post Office to Addressee" service of the United States Postal Service under Mailing Label No. EK916750942US

  
Annya Dushine

**3. Oath or Declaration**

- ☐ Enclosed
- ☐ Executed by (check all applicable boxes)
- ☐ Inventor(s)
- ☐ Legal representative of inventors(s) (37 CFR 1.42 or 1.43)
- ☐ Joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached
- ☐ The petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 are enclosed. See Item 5D below for fee.
- ☒ Unexecuted – the undersigned attorney or agent is authorized to file this application on behalf of the applicant(s). An executed declaration will follow.

**4. Additional Papers Enclosed**

- ☐ Preliminary Amendment
- ☐ Information Disclosure Statement
- ☐ Declaration of Biological Deposit
- ☒ Computer readable copy of sequence listing containing nucleotide and/or amino acid sequence
- ☒ Statement Under 37 CFR § 1.821
- ☒ Paper copy of sequence listing identical to computer copy (575 pages)
- ☐ Microfiche computer program
- ☒ Verified statement claiming small entity status under 37 CFR 1.9 and 1.27
- ☐ Associate Power of Attorney
- ☐ Verified translation of a non-English patent application
- ☒ Return receipt postcard
- ☐ Other \_\_\_\_\_

**5. Priority Applications Under 35 USC 119**

Certified copies of applications from which priority under 35 USC 119 is claimed are listed below and

- ☐ are attached.
- ☐ will follow.



6. **Filing Fee Calculation (37 CFR 1.16)**

A. ☒ **Utility Application**

CLAIMS AS FILED – INCLUDING PRELIMINARY AMENDMENT (IF ANY)						
			SMALL ENTITY		OTHER THAN A SMALL ENTITY	
	NO. FILED	NO. EXTRA	RATE	FEE	RATE	FEE
BASIC FEE				\$345.00		\$690.00
TOTAL	30-20	= 10	X 9 =	\$90.00	X 18 =	\$0.00
INDEP.	3-3	= 0	X 39 =	\$0.00	X 78 =	\$0.00
<input checked="" type="checkbox"/> First Presentation of Multiple Dependent Claim			+ 130 =	\$130.00	+ 260 =	\$0.00
FILING FEE:				\$565.00	OR	\$0.00

B. ☐ **Design Application (\$155.00/\$310.00)** Filing Fee: \$\_\_\_\_\_

C. ☐ **Plant Application (\$240.00/\$480.00)** Filing Fee: \$\_\_\_\_\_

D. **Other fees**

☐ Recording Assignment [Fee -- \$40.00 per assignment] \$\_\_\_\_\_

☐ Other \$\_\_\_\_\_

**TOTAL FEES \$ 565.00**

7. **Method of Payments of Fees**

- ☐ Enclosed check
- ☒ Charge Deposit Account No. 501169. A duplicate copy of this transmittal is enclosed
- ☐ Not enclosed

8. **Deposit Account and Refund Authorization**

The Commissioner is hereby authorized to charge payment of any additional fees due or credit any overpayment to Deposit Account No. 501169. A duplicate copy of this transmittal is enclosed.

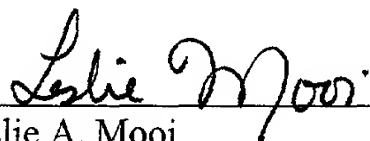
Please refund any overpayment to Hyseq, Inc. at the address below.

Please direct all future correspondence to Leslie A. Mooi at the address below.

Respectfully submitted,

Date: September 01, 2000

By:

  
\_\_\_\_\_  
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant(s) or Patentee(s): Y. Tom Tang, Chenghua Liu, Vinod Asundi, Ping Zhou, Jie Zhang, Feiyan Ren, Qing A. Zhao, Aidong J. Xue, Tom Wehrman, Jian-Rui Wang, Radoje T. Drmanac

Application No. or Patent No.: Not Yet Assigned

Filed or Issued: Herewith

For: NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS  
(37 CFR § 1.9(f) AND 1.27(c)) - SMALL BUSINESS CONCERN**

I hereby declare that I am

- ☐ The owner of the small business concern identified below:  
☒ An official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN: HYSEQ, INC.  
ADDRESS: 670 Almanor Avenue  
Sunnyvale, CA 94085

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR § 121.12, and reproduced in 37 CFR § 1.9(d), for purposes of paying reduced fees under § 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to, and remain with, the small business concern identified above with regard to the invention, entitled NOVEL NUCLEIC ACIDS AND POLYPEPTIDES by inventors Y. Tom Tang, Chenghua Liu, Vinod Asundi, Ping Zhou, Jie Zhang, Feiyan Ren, Qing A. Zhao, Aidong J. Xue, Tom Wehrman, Jian-Rui Wang, Radoje T. Drmanac, et al. described in

- ☒ The specification filed herewith.  
☐ Application Serial No. [ ], filed [Date].  
☐ Patent No. [ ], issued [Date].

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below<sup>1</sup> and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR § 1.9(c), or by any concern which would not qualify as a small business concern under 37 CFR § 1.9(d) or a nonprofit organization under 37 CFR § 1.9(e).

Full Name: \_\_\_\_\_

Address: \_\_\_\_\_

( ) Individual ( ) Small Business Concern ( ) Nonprofit Organization

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate (37 CFR § 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Name of person signing: Mark E. Gitter

Title of person  
other than owner: Chief Financial Officer

Address of person signing: HYSEQ, INC.  
670 Almanor Avenue  
Sunnyvale, CA 94085

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

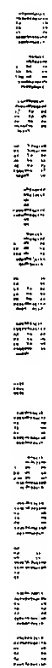
*Mark E. Gitter*  
*9/1/00*

<sup>1</sup>NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR § 1.27)

Our Ref. No.: 787CIP2C



**NOVEL NUCLEIC ACIDS AND POLYPEPTIDES**



Express Mail Label No.: EK916750942US

# NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

## 1. CROSS REFERENCE TO RELATED APPLICATIONS

5           This application is a continuation-in-part application of U.S. Application Serial No. 09/560,875, filed April 27, 2000, Attorney Docket No. 787CIP, which in turn is a continuation-in-part application of U.S. Application Serial No. 09/496,914, filed February 03, 2000, both of which are incorporated herein by reference in their entirety.

## 10   2. BACKGROUND OF THE INVENTION

### 2.1 TECHNICAL FIELD

          The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with uses for these polynucleotides and proteins, for  
15   example in therapeutic, diagnostic and research methods.

### 2.2 BACKGROUND

          Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs, chemokines, and interleukins) has matured  
20   rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as  
25   signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization-based cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity, for example, by virtue of their secreted nature in the

case of leader sequence cloning, by virtue of their cell or tissue source in the case of PCR-based techniques, or by virtue of structural similarity to other genes of known biological activity.

Identified polynucleotide and polypeptide sequences have numerous applications in, for example, diagnostics, forensics, gene mapping; identification of mutations responsible for genetic disorders or other traits, to assess biodiversity, and to produce many other types of data and products dependent on DNA and amino acid sequences.

### 3. SUMMARY OF THE INVENTION

The compositions of the present invention include novel isolated polypeptides, novel isolated polynucleotides encoding such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, antisense polynucleotide molecules, and antibodies that specifically recognize one or more epitopes present on such polypeptides, as well as hybridomas producing such antibodies.

The compositions of the present invention additionally include vectors, including expression vectors, containing the polynucleotides of the invention, cells genetically engineered to contain such polynucleotides and cells genetically engineered to express such polynucleotides.

The present invention relates to a collection or library of at least one novel nucleic acid sequence assembled from expressed sequence tags (ESTs) isolated mainly by sequencing by hybridization (SBH), and in some cases, sequences obtained from one or more public databases. The invention relates also to the proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins. These nucleic acid sequences are designated as SEQ ID NO: 1 – 164 and are provided in the Sequence Listing. In the nucleic acids provided in the Sequence Listing, A is adenosine; C is cytosine; G is guanosine; T is thymine; and N is any of the four bases. In the amino acids provided in the Sequence Listing, \* corresponds to the stop codon.

The nucleic acid sequences of the present invention also include, nucleic acid sequences that hybridize to the complement of SEQ ID NO: 1 – 164 under stringent hybridization conditions; nucleic acid sequences which are allelic variants or species homologues of any of the nucleic acid sequences recited above, or nucleic acid sequences that encode a peptide comprising a specific domain or truncation of the peptides encoded by SEQ ID NO: 1 – 164. A polynucleotide comprising a nucleotide sequence having at least 90% identity to an identifying sequence of SEQ ID NO: 1 – 164 or a degenerate variant or fragment thereof. The identifying sequence can be 100 base pairs in length.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NO: 1 – 164. The sequence information can be a segment of any one of SEQ ID NO: 1 – 164 that uniquely identifies or represents the sequence information of SEQ ID NO: 1 – 164.

A collection as used in this application can be a collection of only one polynucleotide. The collection of sequence information or identifying information of each sequence can be provided on a nucleic acid array. In one embodiment, segments of sequence information is provided on a nucleic acid array to detect the polynucleotide that contains the segment. The array can be designed to detect full-match or mismatch to the polynucleotide that contains the segment. The collection can also be provided in a computer-readable format.

This invention also includes the reverse or direct complement of any of the nucleic acid sequences recited above; cloning or expression vectors containing the nucleic acid sequences; and host cells or organisms transformed with these expression vectors. Nucleic acid sequences (or their reverse or direct complements) according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology, such as use as hybridization probes, use as primers for PCR, use in an array, use in computer-readable media, use in sequencing full-length genes, use for chromosome and gene mapping, use in the recombinant production of protein, and use in the generation of anti-sense DNA or RNA, their chemical analogs and the like.

In a preferred embodiment, the nucleic acid sequences of SEQ ID NO: 1-164 or novel segments or parts of the nucleic acids of the invention are used as primers in



expression assays that are well known in the art. In a particularly preferred embodiment, the nucleic acid sequences of SEQ ID NO: 1-164 or novel segments or parts of the nucleic acids provided herein are used in diagnostics for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The isolated polynucleotides of the invention include, but are not limited to, a polynucleotide comprising any one of the nucleotide sequences set forth in the SEQ ID NO: 1-164; a polynucleotide comprising any of the full length protein coding sequences of the SEQ ID NO: 1-164; and a polynucleotide comprising any of the nucleotide sequences of the mature protein coding sequences of the SEQ ID NO: 1-164. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent hybridization conditions to (a) the complement of any one of the nucleotide sequences set forth in the SEQ ID NO: 1-164; (b) a nucleotide sequence encoding any one of the amino acid sequences set forth in the Sequence Listing; (c) a polynucleotide which is an allelic variant of any polynucleotides recited above; (d) a polynucleotide which encodes a species homolog (e.g. orthologs) of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of any of the polypeptides comprising an amino acid sequence set forth in the Sequence Listing.

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising any of the amino acid sequences set forth in the Sequence Listing; or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides with biological activity that are encoded by (a) any of the polynucleotides having a nucleotide sequence set forth in the SEQ ID NO: 1-164; or (b) polynucleotides that hybridize to the complement of the polynucleotides of (a) under stringent hybridization conditions. Biologically or immunologically active variants of any of the polypeptide sequences in the Sequence Listing, and "substantial equivalents" thereof (e.g., with at least about 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% amino acid sequence identity) that preferably retain biological activity are also contemplated. The polypeptides of the invention may be wholly or partially chemically synthesized but are

preferably produced by recombinant means using the genetically engineered cells (e.g. host cells) of the invention.

The invention also provides compositions comprising a polypeptide of the invention. Polypeptide compositions of the invention may further comprise an acceptable carrier, such as a hydrophilic, e.g., pharmaceutically acceptable, carrier.

The invention also provides host cells transformed or transfected with a polynucleotide of the invention.

The invention also relates to methods for producing a polypeptide of the invention comprising growing a culture of the host cells of the invention in a suitable culture medium under conditions permitting expression of the desired polypeptide, and purifying the polypeptide from the culture or from the host cells. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Polynucleotides according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology. These techniques include use as hybridization probes, use as oligomers, or primers, for PCR, use for chromosome and gene mapping, use in the recombinant production of protein, and use in generation of anti-sense DNA or RNA, their chemical analogs and the like. For example, when the expression of an mRNA is largely restricted to a particular cell or tissue type, polynucleotides of the invention can be used as hybridization probes to detect the presence of the particular cell or tissue mRNA in a sample using, *e.g.*, *in situ* hybridization.

In other exemplary embodiments, the polynucleotides are used in diagnostics as expressed sequence tags for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The polypeptides according to the invention can be used in a variety of conventional procedures and methods that are currently applied to other proteins. For example, a polypeptide of the invention can be used to generate an antibody that specifically binds the polypeptide. Such antibodies, particularly monoclonal antibodies,

are useful for detecting or quantitating the polypeptide in tissue. The polypeptides of the invention can also be used as molecular weight markers, and as a food supplement.

Methods are also provided for preventing, treating, or ameliorating a medical condition which comprises the step of administering to a mammalian subject a  
5 therapeutically effective amount of a composition comprising a polypeptide of the present invention and a pharmaceutically acceptable carrier.

In particular, the polypeptides and polynucleotides of the invention can be utilized, for example, in methods for the prevention and/or treatment of disorders involving aberrant protein expression or biological activity.

10 The present invention further relates to methods for detecting the presence of the polynucleotides or polypeptides of the invention in a sample. Such methods can, for example, be utilized as part of prognostic and diagnostic evaluation of disorders as recited herein and for the identification of subjects exhibiting a predisposition to such conditions. The invention provides a method for detecting the polynucleotides of the  
15 invention in a sample, comprising contacting the sample with a compound that binds to and forms a complex with the polynucleotide of interest for a period sufficient to form the complex and under conditions sufficient to form a complex and detecting the complex such that if a complex is detected, the polynucleotide of interest is detected. The invention also provides a method for detecting the polypeptides of the invention in  
20 a sample comprising contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex and detecting the formation of the complex such that if a complex is formed, the polypeptide is detected.

The invention also provides kits comprising polynucleotide probes and/or  
25 monoclonal antibodies, and optionally quantitative standards, for carrying out methods of the invention. Furthermore, the invention provides methods for evaluating the efficacy of drugs, and monitoring the progress of patients, involved in clinical trials for the treatment of disorders as recited above.

The invention also provides methods for the identification of compounds that  
30 modulate (i.e., increase or decrease) the expression or activity of the polynucleotides

and/or polypeptides of the invention. Such methods can be utilized, for example, for the identification of compounds that can ameliorate symptoms of disorders as recited herein. Such methods can include, but are not limited to, assays for identifying compounds and other substances that interact with (*e.g.*, bind to) the polypeptides of the invention. The invention provides a method for identifying a compound that binds to the polypeptides of the invention comprising contacting the compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and detecting the complex by detecting the reporter gene sequence expression such that if expression of the reporter gene is detected the compound the binds to a polypeptide of the invention is identified.

The methods of the invention also provides methods for treatment which involve the administration of the polynucleotides or polypeptides of the invention to individuals exhibiting symptoms or tendencies. In addition, the invention encompasses methods for treating diseases or disorders as recited herein comprising administering compounds and other substances that modulate the overall activity of the target gene products. Compounds and other substances can effect such modulation either on the level of target gene/protein expression or target protein activity.

The polypeptides of the present invention and the polynucleotides encoding them are also useful for the same functions known to one of skill in the art as the polypeptides and polynucleotides to which they have the closest homology (set forth in Table 1). If no homology is set forth for a sequence, then the polypeptides and polynucleotides of the present invention are useful for a variety of applications, as described herein, including use in arrays for detection.

## 4. DETAILED DESCRIPTION OF THE INVENTION

### 4.1 DEFINITIONS

It must be noted that as used herein and in the appended claims, the singular forms “a”, “an” and “the” include plural references unless the context clearly dictates otherwise.

5 The term "active" refers to those forms of the polypeptide which retain the biologic and/or immunologic activities of any naturally occurring polypeptide. According to the invention, the terms “biologically active” or “biological activity” refer to a protein or peptide having structural, regulatory or biochemical functions of a naturally occurring molecule. Likewise “immunologically active” or “immunological activity” refers to the capability of the natural, recombinant or synthetic polypeptide to  
10 induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The term "activated cells" as used in this application are those cells which are engaged in extracellular or intracellular membrane trafficking, including the export of secretory or enzymatic molecules as part of a normal or disease process.

15 The terms “complementary” or “complementarity” refer to the natural binding of polynucleotides by base pairing. For example, the sequence 5'-AGT-3' binds to the complementary sequence 3'-TCA-5'. Complementarity between two single-stranded molecules may be “partial” such that only some of the nucleic acids bind or it may be “complete” such that total complementarity exists between the single stranded  
20 molecules. The degree of complementarity between the nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands.

The term “embryonic stem cells (ES)” refers to a cell that can give rise to many differentiated cell types in an embryo or an adult, including the germ cells. The term  
25 “germ line stem cells (GSCs)” refers to stem cells derived from primordial stem cells that provide a steady and continuous source of germ cells for the production of gametes. The term “primordial germ cells (PGCs)” refers to a small population of cells set aside from other cell lineages particularly from the yolk sac, mesenteries, or gonadal ridges during embryogenesis that have the potential to differentiate into germ  
30 cells and other cells. PGCs are the source from which GSCs and ES cells are derived

The PGCs, the GSCs and the ES cells are capable of self-renewal. Thus these cells not only populate the germ line and give rise to a plurality of terminally differentiated cells that comprise the adult specialized organs, but are able to regenerate themselves.

The term "expression modulating fragment," EMF, means a series of  
5 nucleotides which modulates the expression of an operably linked ORF or another EMF.

As used herein, a sequence is said to "modulate the expression of an operably linked sequence" when the expression of the sequence is altered by the presence of the EMF. EMFs include, but are not limited to, promoters, and promoter modulating  
10 sequences (inducible elements). One class of EMFs are nucleic acid fragments which induce the expression of an operably linked ORF in response to a specific regulatory factor or physiological event.

The terms "nucleotide sequence" or "nucleic acid" or "polynucleotide" or "oligonucleotide" are used interchangeably and refer to a heteropolymer of nucleotides  
15 or the sequence of these nucleotides. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA) or to any DNA-like or RNA-like material. It is contemplated that where the polynucleotide is RNA, the T (thymine) in the sequences provided herein may be substituted with U  
20 (uracil). Generally, nucleic acid segments provided by this invention may be assembled from fragments of the genome and short oligonucleotide linkers, or from a series of oligonucleotides, or from individual nucleotides, to provide a synthetic nucleic acid which is capable of being expressed in a recombinant transcriptional unit comprising regulatory elements derived from a microbial or viral operon, or a eukaryotic gene.

25 The terms "oligonucleotide fragment" or a "polynucleotide fragment", "portion," or "segment" or "probe" or "primer" are used interchangeably and refer to a sequence of nucleotide residues which are at least about 5 nucleotides, more preferably at least about 7 nucleotides, more preferably at least about 9 nucleotides, more preferably at least about 11 nucleotides and most preferably at least about 17  
30 nucleotides. The fragment is preferably less than about 500 nucleotides, preferably less

than about 200 nucleotides, more preferably less than about 100 nucleotides, more preferably less than about 50 nucleotides and most preferably less than 30 nucleotides. Preferably the probe is from about 6 nucleotides to about 200 nucleotides, preferably from about 15 to about 50 nucleotides, more preferably from about 17 to 30 nucleotides and most preferably from about 20 to 25 nucleotides. Preferably the fragments can be used in polymerase chain reaction (PCR), various hybridization procedures or microarray procedures to identify or amplify identical or related parts of mRNA or DNA molecules. A fragment or segment may uniquely identify each polynucleotide sequence of the present invention. Preferably the fragment comprises a sequence substantially similar to any one of SEQ ID NOs:1-164.

Probes may, for example, be used to determine whether specific mRNA molecules are present in a cell or tissue or to isolate similar nucleic acid sequences from chromosomal DNA as described by Walsh et al. (Walsh, P.S. et al., 1992, PCR Methods Appl 1:241-250). They may be labeled by nick translation, Klenow fill-in reaction, PCR, or other methods well known in the art. Probes of the present invention, their preparation and/or labeling are elaborated in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY; or Ausubel, F.M. et al., 1989, Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, both of which are incorporated herein by reference in their entirety.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NOs: 1-164. The sequence information can be a segment of any one of SEQ ID NOs: 1-164 that uniquely identifies or represents the sequence information of that sequence of SEQ ID NO: 1-164. One such segment can be a twenty-mer nucleic acid sequence because the probability that a twenty-mer is fully matched in the human genome is 1 in 300. In the human genome, there are three billion base pairs in one set of chromosomes. Because  $4^{20}$  possible twenty-mers exist, there are 300 times more twenty-mers than there are base pairs in a set of human chromosome. Using the same analysis, the probability for a seventeen-mer to be fully matched in the human genome is approximately 1 in 5. When these

segments are used in arrays for expression studies, fifteen-mer segments can be used. The probability that the fifteen-mer is fully matched in the expressed sequences is also approximately one in five because expressed sequences comprise less than approximately 5% of the entire genome sequence.

5 Similarly, when using sequence information for detecting a single mismatch, a segment can be a twenty-five mer. The probability that the twenty-five mer would appear in a human genome with a single mismatch is calculated by multiplying the probability for a full match ( $1/4^{25}$ ) times the increased probability for mismatch at each nucleotide position ( $3 \times 25$ ). The probability that an eighteen mer with a single mismatch can be  
10 detected in an array for expression studies is approximately one in five. The probability that a twenty-mer with a single mismatch can be detected in a human genome is approximately one in five.

The term "open reading frame," ORF, means a series of nucleotide triplets coding for amino acids without any termination codons and is a sequence translatable  
15 into protein.

The terms "operably linked" or "operably associated" refer to functionally related nucleic acid sequences. For example, a promoter is operably associated or operably linked with a coding sequence if the promoter controls the transcription of the coding sequence. While operably linked nucleic acid sequences can be contiguous and  
20 in the same reading frame, certain genetic elements e.g. repressor genes are not contiguously linked to the coding sequence but still control transcription/translation of the coding sequence.

The term "pluripotent" refers to the capability of a cell to differentiate into a number of differentiated cell types that are present in an adult organism. A pluripotent  
25 cell is restricted in its differentiation capability in comparison to a totipotent cell.

The terms "polypeptide" or "peptide" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide or protein sequence or fragment thereof and to naturally occurring or synthetic molecules. A polypeptide "fragment," "portion," or "segment" is a stretch of amino acid residues of at least about 5 amino acids, preferably  
30 at least about 7 amino acids, more preferably at least about 9 amino acids and most



preferably at least about 17 or more amino acids. The peptide preferably is not greater than about 200 amino acids, more preferably less than 150 amino acids and most preferably less than 100 amino acids. Preferably the peptide is from about 5 to about 200 amino acids. To be active, any polypeptide must have sufficient length to display biological and/or immunological activity.

The term "naturally occurring polypeptide" refers to polypeptides produced by cells that have not been genetically engineered and specifically contemplates various polypeptides arising from post-translational modifications of the polypeptide including, but not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation.

The term "translated protein coding portion" means a sequence which encodes for the full length protein which may include any leader sequence or any processing sequence.

The term "mature protein coding sequence" means a sequence which encodes a peptide or protein without a signal or leader sequence. The peptide may have been produced by processing in the cell which removes any leader/signal sequence. The peptide may be produced synthetically or the protein may have been produced using a polynucleotide only encoding for the mature protein coding sequence.

The term "derivative" refers to polypeptides chemically modified by such techniques as ubiquitination, labeling (e.g., with radionuclides or various enzymes), covalent polymer attachment such as pegylation (derivatization with polyethylene glycol) and insertion or substitution by chemical synthesis of amino acids such as ornithine, which do not normally occur in human proteins.

The term "variant"(or "analog") refers to any polypeptide differing from naturally occurring polypeptides by amino acid insertions, deletions, and substitutions, created using, *e.g.*, recombinant DNA techniques. Guidance in determining which amino acid residues may be replaced, added or deleted without abolishing activities of interest, may be found by comparing the sequence of the particular polypeptide with that of homologous peptides and minimizing the number of amino acid sequence

changes made in regions of high homology (conserved regions) or by replacing amino acids with consensus sequence.

Alternatively, recombinant variants encoding these same or similar polypeptides may be synthesized or selected by making use of the "redundancy" in the genetic code.

5 Various codon substitutions, such as the silent changes which produce various restriction sites, may be introduced to optimize cloning into a plasmid or viral vector or expression in a particular prokaryotic or eukaryotic system. Mutations in the polynucleotide sequence may be reflected in the polypeptide or domains of other peptides added to the polypeptide to modify the properties of any part of the  
10 polypeptide, to change characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate.

Preferably, amino acid "substitutions" are the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, *i.e.*, conservative amino acid replacements. "Conservative" amino acid substitutions may be  
15 made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively  
20 charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid. "Insertions" or "deletions" are preferably in the range of about 1 to 20 amino acids, more preferably 1 to 10 amino acids. The variation allowed may be experimentally determined by systematically making insertions, deletions, or substitutions of amino acids in a  
25 polypeptide molecule using recombinant DNA techniques and assaying the resulting recombinant variants for activity.

Alternatively, where alteration of function is desired, insertions, deletions or non-conservative alterations can be engineered to produce altered polypeptides. Such alterations can, for example, alter one or more of the biological functions or  
30 biochemical characteristics of the polypeptides of the invention. For example, such

alterations may change polypeptide characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate. Further, such alterations can be selected so as to generate polypeptides that are better suited for expression, scale up and the like in the host cells chosen for expression. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges.

The terms "purified" or "substantially purified" as used herein denotes that the indicated nucleic acid or polypeptide is present in the substantial absence of other biological macromolecules, *e.g.*, polynucleotides, proteins, and the like. In one embodiment, the polynucleotide or polypeptide is purified such that it constitutes at least 95% by weight, more preferably at least 99% by weight, of the indicated biological macromolecules present (but water, buffers, and other small molecules, especially molecules having a molecular weight of less than 1000 daltons, can be present).

The term "isolated" as used herein refers to a nucleic acid or polypeptide separated from at least one other component (*e.g.*, nucleic acid or polypeptide) present with the nucleic acid or polypeptide in its natural source. In one embodiment, the nucleic acid or polypeptide is found in the presence of (if anything) only a solvent, buffer, ion, or other component normally present in a solution of the same. The terms "isolated" and "purified" do not encompass nucleic acids or polypeptides present in their natural source.

The term "recombinant," when used herein to refer to a polypeptide or protein, means that a polypeptide or protein is derived from recombinant (*e.g.*, microbial, insect, or mammalian) expression systems. "Microbial" refers to recombinant polypeptides or proteins made in bacterial or fungal (*e.g.*, yeast) expression systems. As a product, "recombinant microbial" defines a polypeptide or protein essentially free of native endogenous substances and unaccompanied by associated native glycosylation. Polypeptides or proteins expressed in most bacterial cultures, *e.g.*, *E. coli*, will be free of glycosylation modifications; polypeptides or proteins expressed in yeast will have a glycosylation pattern in general different from those expressed in mammalian cells.

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The term "recombinant expression vehicle or vector" refers to a plasmid or phage or virus or vector, for expressing a polypeptide from a DNA (RNA) sequence. An expression vehicle can comprise a transcriptional unit comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or coding sequence which is transcribed into mRNA and translated into protein, and (3) appropriate transcription initiation and termination sequences. Structural units intended for use in yeast or eukaryotic expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where recombinant protein is expressed without a leader or transport sequence, it may include an amino terminal methionine residue. This residue may or may not be subsequently cleaved from the expressed recombinant protein to provide a final product.

The term "recombinant expression system" means host cells which have stably integrated a recombinant transcriptional unit into chromosomal DNA or carry the recombinant transcriptional unit extrachromosomally. Recombinant expression systems as defined herein will express heterologous polypeptides or proteins upon induction of the regulatory elements linked to the DNA segment or synthetic gene to be expressed. This term also means host cells which have stably integrated a recombinant genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers. Recombinant expression systems as defined herein will express polypeptides or proteins endogenous to the cell upon induction of the regulatory elements linked to the endogenous DNA segment or gene to be expressed. The cells can be prokaryotic or eukaryotic.

The term "secreted" includes a protein that is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence when it is expressed in a suitable host cell. "Secreted" proteins include without limitation proteins secreted wholly (*e.g.*, soluble proteins) or partially (*e.g.*, receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins that are transported across the membrane of the endoplasmic reticulum. "Secreted" proteins are also intended to include proteins containing

non-typical signal sequences (e.g. Interleukin-1 Beta, see Krasney, P.A. and Young, P.R. (1992) Cytokine 4(2):134 -143) and factors released from damaged cells (e.g. Interleukin-1 Receptor Antagonist, see Arend, W.P. et. al. (1998) Annu. Rev. Immunol. 16:27-55)

5           Where desired, an expression vector may be designed to contain a "signal or leader sequence" which will direct the polypeptide through the membrane of a cell. Such a sequence may be naturally present on the polypeptides of the present invention or provided from heterologous protein sources by recombinant DNA techniques.

10           The term "stringent" is used to refer to conditions that are commonly understood in the art as stringent. Stringent conditions can include highly stringent conditions (i.e., hybridization to filter-bound DNA in 0.5 M NaHPO<sub>4</sub>, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1X SSC/0.1% SDS at 68°C), and moderately stringent conditions (i.e., washing in 0.2X SSC/0.1% SDS at 42°C). Other exemplary hybridization conditions are described herein in the examples.

15           In instances of hybridization of deoxyoligonucleotides, additional exemplary stringent hybridization conditions include washing in 6X SSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligonucleotides), 48°C (for 17-base oligos), 55°C (for 20-base oligonucleotides), and 60°C (for 23-base oligonucleotides).

20           As used herein, "substantially equivalent" can refer both to nucleotide and amino acid sequences, for example a mutant sequence, that varies from a reference sequence by one or more substitutions, deletions, or additions, the net effect of which does not result in an adverse functional dissimilarity between the reference and subject sequences. Typically, such a substantially equivalent sequence varies from one of those listed herein by no more than about 35% (*i.e.*, the number of individual residue  
25       substitutions, additions, and/or deletions in a substantially equivalent sequence, as compared to the corresponding reference sequence, divided by the total number of residues in the substantially equivalent sequence is about 0.35 or less). Such a sequence is said to have 65% sequence identity to the listed sequence. In one embodiment, a substantially equivalent, *e.g.*, mutant, sequence of the invention varies  
30       from a listed sequence by no more than 30% (70% sequence identity); in a variation of

this embodiment, by no more than 25% (75% sequence identity); and in a further variation of this embodiment, by no more than 20% (80% sequence identity) and in a further variation of this embodiment, by no more than 10% (90% sequence identity) and in a further variation of this embodiment, by no more than 5% (95% sequence identity). Substantially equivalent, *e.g.*, mutant, amino acid sequences according to the invention preferably have at least 80% sequence identity with a listed amino acid sequence, more preferably at least 90% sequence identity. Substantially equivalent nucleotide sequences of the invention can have lower percent sequence identities, taking into account, for example, the redundancy or degeneracy of the genetic code.

Preferably, nucleotide sequence has at least about 65% identity, more preferably at least about 75% identity, and most preferably at least about 95% identity. For the purposes of the present invention, sequences having substantially equivalent biological activity and substantially equivalent expression characteristics are considered substantially equivalent. For the purposes of determining equivalence, truncation of the mature sequence (*e.g.*, via a mutation which creates a spurious stop codon) should be disregarded. Sequence identity may be determined, *e.g.*, using the Jotun Hein method (Hein, J. (1990) *Methods Enzymol.* 183:626-645). Identity between sequences can also be determined by other methods known in the art, *e.g.* by varying hybridization conditions.

The term "totipotent" refers to the capability of a cell to differentiate into all of the cell types of an adult organism.

The term "transformation" means introducing DNA into a suitable host cell so that the DNA is replicable, either as an extrachromosomal element, or by chromosomal integration. The term "transfection" refers to the taking up of an expression vector by a suitable host cell, whether or not any coding sequences are in fact expressed. The term "infection" refers to the introduction of nucleic acids into a suitable host cell by use of a virus or viral vector.

As used herein, an "uptake modulating fragment," UMF, means a series of nucleotides which mediate the uptake of a linked DNA fragment into a cell. UMFs can be readily identified using known UMFs as a target sequence or target motif with the

computer-based systems described below. The presence and activity of a UMF can be confirmed by attaching the suspected UMF to a marker sequence. The resulting nucleic acid molecule is then incubated with an appropriate host under appropriate conditions and the uptake of the marker sequence is determined. As described above, a UMF will increase the frequency of uptake of a linked marker sequence.

Each of the above terms is meant to encompass all that is described for each, unless the context dictates otherwise.

## 4.2 NUCLEIC ACIDS OF THE INVENTION

Nucleotide sequences of the invention are set forth in the Sequence Listing.

The isolated polynucleotides of the invention include a polynucleotide comprising the nucleotide sequences of the SEQ ID NO: 1 – 164; a polynucleotide encoding any one of the peptide sequences of SEQ ID NO:1 – 164; and a polynucleotide comprising the nucleotide sequence encoding the mature protein coding sequence of the polynucleotides of any one of SEQ ID NO: 1 - 164. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent conditions to (a) the complement of any of the nucleotides sequences of the SEQ ID NO: 1 – 164; (b) nucleotide sequences encoding any one of the amino acid sequences set forth in the Sequence Listing; (c) a polynucleotide which is an allelic variant of any polynucleotide recited above; (d) a polynucleotide which encodes a species homolog of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of the polypeptides of SEQ ID NO: 1- 164. Domains of interest may depend on the nature of the encoded polypeptide; e.g., domains in receptor-like polypeptides include ligand-binding, extracellular, transmembrane, or cytoplasmic domains, or combinations thereof; domains in immunoglobulin-like proteins include the variable immunoglobulin-like domains; domains in enzyme-like polypeptides include catalytic and substrate binding domains; and domains in ligand polypeptides include receptor-binding domains.

The polynucleotides of the invention include naturally occurring or wholly or partially synthetic DNA, e.g., cDNA and genomic DNA, and RNA, e.g., mRNA. The polynucleotides may include all of the coding region of the cDNA or may represent a portion of the coding region of the cDNA.

5 The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other  
10 sources of genomic materials. Further 5' and 3' sequence can be obtained using methods known in the art. For example, full length cDNA or genomic DNA that corresponds to any of the polynucleotides of the SEQ ID NO: 1 - 164 can be obtained by screening appropriate cDNA or genomic DNA libraries under suitable hybridization conditions using any of the polynucleotides of the SEQ ID NO: 1 - 164 or a portion thereof as a probe.  
15 Alternatively, the polynucleotides of the SEQ ID NO: 1 - 164 may be used as the basis for suitable primer(s) that allow identification and/or amplification of genes in appropriate genomic DNA or cDNA libraries.

The nucleic acid sequences of the invention can be assembled from ESTs and sequences (including cDNA and genomic sequences) obtained from one or more public  
20 databases, such as dbEST, gbpri, and UniGene. The EST sequences can provide identifying sequence information, representative fragment or segment information, or novel segment information for the full-length gene.

The polynucleotides of the invention also provide polynucleotides including nucleotide sequences that are substantially equivalent to the polynucleotides recited  
25 above. Polynucleotides according to the invention can have, e.g., at least about 65%, at least about 70%, at least about 75%, at least about 80%, more typically at least about 90%, and even more typically at least about 95%, sequence identity to a polynucleotide recited above.

Included within the scope of the nucleic acid sequences of the invention are  
30 nucleic acid sequence fragments that hybridize under stringent conditions to any of the



nucleotide sequences of the SEQ ID NO: 1 - 164, or complements thereof, which fragment is greater than about 5 nucleotides, preferably 7 nucleotides, more preferably greater than 9 nucleotides and most preferably greater than 17 nucleotides. Fragments of, e.g. 15, 17, or 20 nucleotides or more that are selective for (i.e. specifically hybridize to any one of the polynucleotides of the invention) are contemplated. Probes capable of specifically hybridizing to a polynucleotide can differentiate polynucleotide sequences of the invention from other polynucleotide sequences in the same family of genes or can differentiate human genes from genes of other species, and are preferably based on unique nucleotide sequences.

The sequences falling within the scope of the present invention are not limited to these specific sequences, but also include allelic and species variations thereof. Allelic and species variations can be routinely determined by comparing the sequence provided in SEQ ID NO: 1 - 164, a representative fragment thereof, or a nucleotide sequence at least 90% identical, preferably 95% identical, to SEQ ID NOs: 1 - 164 with a sequence from another isolate of the same species. Furthermore, to accommodate codon variability, the invention includes nucleic acid molecules coding for the same amino acid sequences as do the specific ORFs disclosed herein. In other words, in the coding region of an ORF, substitution of one codon for another codon that encodes the same amino acid is expressly contemplated.

The nearest neighbor result for the nucleic acids of the present invention, including SEQ ID NOs: 1 - 164, can be obtained by searching a database using an algorithm or a program. Preferably, a BLAST which stands for Basic Local Alignment Search Tool is used to search for local sequence alignments (Altshul, S.F. J Mol. Evol. 36 290-300 (1993) and Altschul S.F. et al. J. Mol. Biol. 21:403-410 (1990)). Alternatively a FASTA version 3 search against Genpept, using Fastxy algorithm.

Species homologs (or orthologs) of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides.

5       The nucleic acid sequences of the invention are further directed to sequences which encode variants of the described nucleic acids. These amino acid sequence variants may be prepared by methods known in the art by introducing appropriate nucleotide changes into a native or variant polynucleotide. There are two variables in the construction of amino acid sequence variants: the location of the mutation and the  
10       nature of the mutation. Nucleic acids encoding the amino acid sequence variants are preferably constructed by mutating the polynucleotide to encode an amino acid sequence that does not occur in nature. These nucleic acid alterations can be made at sites that differ in the nucleic acids from different species (variable positions) or in highly conserved regions (constant regions). Sites at such locations will typically be  
15       modified in series, *e.g.*, by substituting first with conservative choices (*e.g.*, hydrophobic amino acid to a different hydrophobic amino acid) and then with more distant choices (*e.g.*, hydrophobic amino acid to a charged amino acid), and then deletions or insertions may be made at the target site. Amino acid sequence deletions generally range from about 1 to 30 residues, preferably about 1 to 10 residues, and are  
20       typically contiguous. Amino acid insertions include amino- and/or carboxyl-terminal fusions ranging in length from one to one hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Intrasequence insertions may range generally from about 1 to 10 amino residues, preferably from 1 to 5 residues. Examples of terminal insertions include the heterologous signal sequences  
25       necessary for secretion or for intracellular targeting in different host cells and sequences such as FLAG or poly-histidine sequences useful for purifying the expressed protein.

In a preferred method, polynucleotides encoding the novel amino acid sequences are changed via site-directed mutagenesis. This method uses oligonucleotide sequences  
30       to alter a polynucleotide to encode the desired amino acid variant, as well as sufficient

adjacent nucleotides on both sides of the changed amino acid to form a stable duplex on either side of the site of being changed. In general, the techniques of site-directed mutagenesis are well known to those of skill in the art and this technique is exemplified by publications such as, Edelman et al., *DNA* 2:183 (1983). A versatile and efficient method for producing site-specific changes in a polynucleotide sequence was published by Zoller and Smith, *Nucleic Acids Res.* 10:6487-6500 (1982). PCR may also be used to create amino acid sequence variants of the novel nucleic acids. When small amounts of template DNA are used as starting material, primer(s) that differs slightly in sequence from the corresponding region in the template DNA can generate the desired amino acid variant. PCR amplification results in a population of product DNA fragments that differ from the polynucleotide template encoding the polypeptide at the position specified by the primer. The product DNA fragments replace the corresponding region in the plasmid and this gives a polynucleotide encoding the desired amino acid variant.

A further technique for generating amino acid variants is the cassette mutagenesis technique described in Wells et al., *Gene* 34:315 (1985); and other mutagenesis techniques well known in the art, such as, for example, the techniques in Sambrook et al., supra, and *Current Protocols in Molecular Biology*, Ausubel et al. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be used in the practice of the invention for the cloning and expression of these novel nucleic acids. Such DNA sequences include those which are capable of hybridizing to the appropriate novel nucleic acid sequence under stringent conditions.

Polynucleotides encoding preferred polypeptide truncations of the invention can be used to generate polynucleotides encoding chimeric or fusion proteins comprising one or more domains of the invention and heterologous protein sequences.

The polynucleotides of the invention additionally include the complement of any of the polynucleotides recited above. The polynucleotide can be DNA (genomic, cDNA, amplified, or synthetic) or RNA. Methods and algorithms for obtaining such polynucleotides are well known to those of skill in the art and can include, for example,

methods for determining hybridization conditions that can routinely isolate polynucleotides of the desired sequence identities.

5 In accordance with the invention, polynucleotide sequences comprising the mature protein coding sequences corresponding to any one of SEQ ID NO: 1-164, or functional equivalents thereof, may be used to generate recombinant DNA molecules that direct the expression of that nucleic acid, or a functional equivalent thereof, in appropriate host cells. Also included are the cDNA inserts of any of the clones identified herein.

10 A polynucleotide according to the invention can be joined to any of a variety of other nucleotide sequences by well-established recombinant DNA techniques (see Sambrook J et al. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY). Useful nucleotide sequences for joining to polynucleotides include an assortment of vectors, e.g., plasmids, cosmids, lambda phage derivatives, phagemids, and the like, that are well known in the art. Accordingly, the invention  
15 also provides a vector including a polynucleotide of the invention and a host cell containing the polynucleotide. In general, the vector contains an origin of replication functional in at least one organism, convenient restriction endonuclease sites, and a selectable marker for the host cell. Vectors according to the invention include expression vectors, replication vectors, probe generation vectors, and sequencing  
20 vectors. A host cell according to the invention can be a prokaryotic or eukaryotic cell and can be a unicellular organism or part of a multicellular organism.

The present invention further provides recombinant constructs comprising a nucleic acid having any of the nucleotide sequences of the SEQ ID NOs: 1 - 164 or a fragment thereof or any other polynucleotides of the invention. In one embodiment, the  
25 recombinant constructs of the present invention comprise a vector, such as a plasmid or viral vector, into which a nucleic acid having any of the nucleotide sequences of the SEQ ID NOs: 1 - 164 or a fragment thereof is inserted, in a forward or reverse orientation. In the case of a vector comprising one of the ORFs of the present invention, the vector may further comprise regulatory sequences, including for  
30 example, a promoter, operably linked to the ORF. Large numbers of suitable vectors

and promoters are known to those of skill in the art and are commercially available for generating the recombinant constructs of the present invention. The following vectors are provided by way of example. Bacterial: pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, 5 pKK233-3, pDR540, pRIT5 (Pharmacia). Eukaryotic: pWLneo, pSV2cat, pOG44, PXTI, pSG (Stratagene) pSVK3, pBPV, pMSG, pSVL (Pharmacia).

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman et al., *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the 10 protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the 15 protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters 20 include lacI, lacZ, T3, T7, gpt, lambda PR, and trc. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art. Generally, recombinant expression vectors will include origins of replication and selectable markers permitting 25 transformation of the host cell, *e.g.*, the ampicillin resistance gene of *E. coli* and *S. cerevisiae* TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), a-factor, acid phosphatase, or heat shock proteins, among others. The heterologous 30 structural sequence is assembled in appropriate phase with translation initiation and

termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an amino terminal identification peptide imparting desired characteristics, *e.g.*, stabilization or simplified purification of expressed recombinant product. Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium* and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*, although others may also be employed as a matter of choice.

As a representative but non-limiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM 1 (Promega Biotech, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced or derepressed by appropriate means (*e.g.*, temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

Polynucleotides of the invention can also be used to induce immune responses. For example, as described in Fan et al., *Nat. Biotech.* 17:870-872 (1999), incorporated herein by reference, nucleic acid sequences encoding a polypeptide may be used to generate antibodies against the encoded polypeptide following topical administration of naked plasmid DNA or following injection, and preferably intramuscular injection of

the DNA. The nucleic acid sequences are preferably inserted in a recombinant expression vector and may be in the form of naked DNA.

### 4.3 HOSTS

5           The present invention further provides host cells genetically engineered to contain the polynucleotides of the invention. For example, such host cells may contain nucleic acids of the invention introduced into the host cell using known transformation, transfection or infection methods. The present invention still further provides host cells genetically engineered to express the polynucleotides of the invention, wherein such  
10 polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in the cell.

Knowledge of nucleic acid sequences allows for modification of cells to permit, or increase, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing,  
15 in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the polypeptide at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the encoding sequences. See, for example, PCT International Publication No. WO94/12650, PCT International Publication No. WO92/20808, and PCT International Publication No.  
20 WO91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., *ada*, *dhfr*, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the coding sequence, amplification of the marker DNA by standard selection  
25 methods results in co-amplification of the desired protein coding sequences in the cells.

The host cell can be a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the recombinant construct into the host cell can be effected by calcium phosphate transfection, DEAE, dextran mediated  
30 transfection, or electroporation (Davis, L. et al., *Basic Methods in Molecular Biology*

(1986)). The host cells containing one of the polynucleotides of the invention, can be used in conventional manners to produce the gene product encoded by the isolated fragment (in the case of an ORF) or can be used to produce a heterologous protein under the control of the EMF.

5 Any host/vector system can be used to express one or more of the ORFs of the present invention. These include, but are not limited to, eukaryotic hosts such as HeLa cells, Cv-1 cell, COS cells, 293 cells, and Sf9 cells, as well as prokaryotic host such as *E. coli* and *B. subtilis*. The most preferred cells are those which do not normally express the particular polypeptide or protein or which expresses the polypeptide or  
10 protein at low natural level. Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et  
15 al., in *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor, New York (1989), the disclosure of which is hereby incorporated by reference.

Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts, described by Gluzman, *Cell* 23:175 (1981). Other  
20 cell lines capable of expressing a compatible vector are, for example, the C127, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60,  
25 U937, HaK or Jurkat cells. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early promoter, enhancer, splice,  
30 and polyadenylation sites may be used to provide the required nontranscribed genetic



elements. Recombinant polypeptides and proteins produced in bacterial culture are usually isolated by initial extraction from cell pellets, followed by one or more salting-out, aqueous ion exchange or size exclusion chromatography steps. Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or insects or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequence include polyadenylation

signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, *e.g.*, inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the host cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

#### 4.4 POLYPEPTIDES OF THE INVENTION

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising: the amino acid sequences set forth as any one of SEQ ID NO: 1-164 or an amino acid sequence encoded by any one of the nucleotide sequences SEQ ID NOs: 1 - 164 or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides preferably with biological or immunological activity that are encoded by: (a) a polynucleotide having any one of the nucleotide sequences set forth in the SEQ ID NOs: 1 - 164 or (b) polynucleotides encoding any one of the amino acid sequences set forth as SEQ ID NO: 1-164 or (c) polynucleotides that hybridize to the complement of the polynucleotides of either (a) or (b) under stringent hybridization conditions. The invention also provides biologically active or immunologically active variants of any of the amino acid sequences set forth as SEQ ID NO: 1-164 or the corresponding full length or mature protein; and "substantial equivalents" thereof (e.g., with at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, typically at least about 95%, more typically at least about 98%, or most typically at least about 99% amino acid identity) that retain biological activity. Polypeptides encoded by allelic variants may have a similar, increased, or decreased activity compared to polypeptides comprising SEQ ID NO: 1-164.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H. U. Saragovi, et al., *Bio/Technology* 10, 773-778 (1992) and in R. S. McDowell, et al., *J. Amer. Chem. Soc.* 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites.

The present invention also provides both full-length and mature forms (for example, without a signal sequence or precursor sequence) of the disclosed proteins.

The protein coding sequence is identified in the sequence listing by translation of the

disclosed nucleotide sequences. The mature form of such protein may be obtained by expression of a full-length polynucleotide in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein is also determinable from the amino acid sequence of the full-length form. Where proteins of the present invention are membrane bound, soluble forms of the proteins are also provided. In such forms, part or all of the regions causing the proteins to be membrane bound are deleted so that the proteins are fully secreted from the cell in which it is expressed.

Protein compositions of the present invention may further comprise an acceptable carrier, such as a hydrophilic, *e.g.*, pharmaceutically acceptable, carrier.

The present invention further provides isolated polypeptides encoded by the nucleic acid fragments of the present invention or by degenerate variants of the nucleic acid fragments of the present invention. By "degenerate variant" is intended nucleotide fragments which differ from a nucleic acid fragment of the present invention (*e.g.*, an ORF) by nucleotide sequence but, due to the degeneracy of the genetic code, encode an identical polypeptide sequence. Preferred nucleic acid fragments of the present invention are the ORFs that encode proteins.

A variety of methodologies known in the art can be utilized to obtain any one of the isolated polypeptides or proteins of the present invention. At the simplest level, the amino acid sequence can be synthesized using commercially available peptide synthesizers. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. This technique is particularly useful in producing small peptides and fragments of larger polypeptides. Fragments are useful, for example, in generating antibodies against the native polypeptide. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The polypeptides and proteins of the present invention can alternatively be purified from cells which have been altered to express the desired polypeptide or

protein. As used herein, a cell is said to be altered to express a desired polypeptide or protein when the cell, through genetic manipulation, is made to produce a polypeptide or protein which it normally does not produce or which the cell normally produces at a lower level. One skilled in the art can readily adapt procedures for introducing and  
5 expressing either recombinant or synthetic sequences into eukaryotic or prokaryotic cells in order to generate a cell which produces one of the polypeptides or proteins of the present invention.

The invention also relates to methods for producing a polypeptide comprising growing a culture of host cells of the invention in a suitable culture medium, and  
10 purifying the protein from the cells or the culture in which the cells are grown. For example, the methods of the invention include a process for producing a polypeptide in which a host cell containing a suitable expression vector that includes a polynucleotide of the invention is cultured under conditions that allow expression of the encoded polypeptide. The polypeptide can be recovered from the culture, conveniently from the  
15 culture medium, or from a lysate prepared from the host cells and further purified. Preferred embodiments include those in which the protein produced by such process is a full length or mature form of the protein.

In an alternative method, the polypeptide or protein is purified from bacterial cells which naturally produce the polypeptide or protein. One skilled in the art can  
20 readily follow known methods for isolating polypeptides and proteins in order to obtain one of the isolated polypeptides or proteins of the present invention. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography, and immuno-affinity chromatography. See, *e.g.*,  
Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag (1994);  
25 Sambrook, et al., in *Molecular Cloning: A Laboratory Manual*; Ausubel et al., *Current Protocols in Molecular Biology*. Polypeptide fragments that retain biological/immunological activity include fragments comprising greater than about 100 amino acids, or greater than about 200 amino acids, and fragments that encode specific protein domains.

The purified polypeptides can be used in *in vitro* binding assays which are well known in the art to identify molecules which bind to the polypeptides. These molecules include but are not limited to, for e.g., small molecules, molecules from combinatorial libraries, antibodies or other proteins. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

In addition, the peptides of the invention or molecules capable of binding to the peptides may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for SEQ ID NO: 1-164.

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications, in the peptide or DNA sequence, can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule.

Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Pat. No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein. Regions of the protein that are important for the protein function can be determined by various methods known in the art including the alanine-scanning method which involved systematic substitution of single or strings of amino acids with alanine,

followed by testing the resulting alanine-containing variant for biological activity. This type of analysis determines the importance of the substituted amino acid(s) in biological activity. Regions of the protein that are important for protein function may be determined by the eMATRIX program.

5 Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and are useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are encompassed by the present invention.

10 The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, Calif., U.S.A. (the MaxBat™ kit), and such methods  
15 are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells  
20 under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (*i.e.*, from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over  
25 such affinity resins as concanavalin A-agarose, heparin-toyopearl™ or Cibacrom blue 3GA Sepharose™; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form  
30 which will facilitate purification. For example, it may be expressed as a fusion protein,

such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX), or as a His tag. Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, Mass.), Pharmacia (Piscataway, N.J.) and Invitrogen, respectively. The protein can also be  
5 tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("FLAG®") is commercially available from Kodak (New Haven, Conn.).

Finally, one or more reverse-phase high performance liquid chromatography (RP- HPLC) steps employing hydrophobic RP-HPLC media, *e.g.*, silica gel having  
10 pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

15 The polypeptides of the invention include analogs (variants). This embraces fragments, as well as peptides in which one or more amino acids has been deleted, inserted, or substituted. Also, analogs of the polypeptides of the invention embrace fusions of the polypeptides or modifications of the polypeptides of the invention, wherein the polypeptide or analog is fused to another moiety or moieties, *e.g.*, targeting  
20 moiety or another therapeutic agent. Such analogs may exhibit improved properties such as activity and/or stability. Examples of moieties which may be fused to the polypeptide or an analog include, for example, targeting moieties which provide for the delivery of polypeptide to pancreatic cells, *e.g.*, antibodies to pancreatic cells, antibodies to immune cells such as T-cells, monocytes, dendritic cells, granulocytes,  
25 etc., as well as receptor and ligands expressed on pancreatic or immune cells. Other moieties which may be fused to the polypeptide include therapeutic agents which are used for treatment, for example, immunosuppressive drugs such as cyclosporin, SK506, azathioprine, CD3 antibodies and steroids. Also, polypeptides may be fused to immune modulators, and other cytokines such as alpha or beta interferon.

30



#### 4.4.1 DETERMINING POLYPEPTIDE AND POLYNUCLEOTIDE IDENTITY AND SIMILARITY

Preferred identity and/or similarity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in computer programs including, but are not limited to, the GCG program package, including GAP (Devereux, J., et al., Nucleic Acids Research 12(1):387 (1984); Genetics Computer Group, University of Wisconsin, Madison, WI), BLASTP, BLASTN, BLASTX, FASTA (Altschul, S.F. et al., J. Molec. Biol. 215:403-410 (1990), PSI-BLAST (Altschul S.F. et al., Nucleic Acids Res. vol. 25, pp. 3389-3402, herein incorporated by reference), eMatrix software (Wu et al., J. Comp. Biol., vol. 6, pp. 219-235 (1999), herein incorporated by reference), eMotif software (Nevill-Manning et al, ISMB-97, vol 4, pp. 202-209, herein incorporated by reference) and the Kyte-Doolittle hydrophobicity prediction algorithm (J. Mol Biol, 157, pp. 105-31 (1982), incorporated herein by reference). The BLAST programs are publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul, S., et al. NCB NLM NIH Bethesda, MD 20894; Altschul, S., et al., J. Mol. Biol. 215:403-410 (1990).

#### 4.5 GENE THERAPY

Mutations in the polynucleotides of the invention gene may result in loss of normal function of the encoded protein. The invention thus provides gene therapy to restore normal activity of the polypeptides of the invention; or to treat disease states involving polypeptides of the invention. Delivery of a functional gene encoding polypeptides of the invention to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, and more particularly viral vectors (e.g., adenovirus, adeno-associated virus, or a retrovirus), or *ex vivo* by use of physical DNA transfer methods (e.g., liposomes or chemical treatments). See, for example, Anderson, Nature, supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, Science, 244: 1275-1281 (1989); Verma, Scientific American: 68-84 (1990); and Miller, Nature, 357: 455-460 (1992). Introduction of any

one of the nucleotides of the present invention or a gene encoding the polypeptides of the present invention can also be accomplished with extrachromosomal substrates (transient expression) or artificial chromosomes (stable expression). Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes. Alternatively, it is contemplated that in other human disease states, preventing the expression of or inhibiting the activity of polypeptides of the invention will be useful in treating the disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of polypeptides of the invention.

Other methods inhibiting expression of a protein include the introduction of antisense molecules to the nucleic acids of the present invention, their complements, or their translated RNA sequences, by methods known in the art. Further, the polypeptides of the present invention can be inhibited by using targeted deletion methods, or the insertion of a negative regulatory element such as a silencer, which is tissue specific.

The present invention still further provides cells genetically engineered *in vivo* to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in the cell. These methods can be used to increase or decrease the expression of the polynucleotides of the present invention.

Knowledge of DNA sequences provided by the invention allows for modification of cells to permit, increase, or decrease, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the protein at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the desired protein encoding sequences. See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., *ada*, *dhfr*, and the multifunctional CAD

gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the desired protein coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the desired protein coding sequences in the cells.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequences include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, *e.g.*, inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of

cells in which the exogenous DNA has integrated into the cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker  
5 flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

10 The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is  
15 incorporated by reference herein in its entirety.

#### 4.6 TRANSGENIC ANIMALS

In preferred methods to determine biological functions of the polypeptides of the invention in vivo, one or more genes provided by the invention are either over  
20 expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals.  
25 Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably

non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of a promoter of the polynucleotides of the invention is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

The polynucleotides of the present invention also make possible the development, through, e.g., homologous recombination or knock out strategies, of animals that fail to express polypeptides of the invention or that express a variant polypeptide. Such animals are useful as models for studying the *in vivo* activities of polypeptide as well as for studying modulators of the polypeptides of the invention.

In preferred methods to determine biological functions of the polypeptides of the invention *in vivo*, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of the polynucleotides of the invention promoter is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

#### 4.7 USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified herein. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA). The mechanism underlying the particular condition or pathology will dictate whether the polypeptides of the invention, the polynucleotides of the invention or modulators (activators or inhibitors) thereof would be beneficial to the subject in need of treatment. Thus, "therapeutic compositions of the invention" include compositions comprising isolated polynucleotides (including recombinant DNA molecules, cloned genes and degenerate variants thereof) or polypeptides of the invention (including full length protein, mature protein and truncations or domains thereof), or compounds and other substances that modulate the overall activity of the target gene products, either at the level of target gene/protein expression or target protein activity. Such modulators include polypeptides, analogs, (variants), including fragments and fusion proteins, antibodies and other binding proteins; chemical compounds that directly or indirectly activate or inhibit the polypeptides of the invention (identified, e.g., via drug screening assays as described herein); antisense polynucleotides and polynucleotides suitable for triple helix

formation; and in particular antibodies or other binding partners that specifically recognize one or more epitopes of the polypeptides of the invention.

The polypeptides of the present invention may likewise be involved in cellular activation or in one of the other physiological pathways described herein.

5

#### 4.7.1 RESEARCH USES AND UTILITIES

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for  
10 tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as  
15 probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein  
20 antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to  
25 identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as  
30 a reagent (including the labeled reagent) in assays designed to quantitatively determine

levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding polypeptide is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

#### 4.7.2 NUTRITIONAL USES

Polynucleotides and polypeptides of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the polypeptide or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the polypeptide or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

#### 4.7.3 CYTOKINE AND CELL PROLIFERATION/DIFFERENTIATION ACTIVITY

A polypeptide of the present invention may exhibit activity relating to cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell



populations. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor-dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of therapeutic compositions of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+(preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e, CMK, HUVEC, and Caco. Therapeutic compositions of the invention can be used in the following:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., I. Immunol. 149:3778-3783, 1992; Bowman et al., I. Immunol. 152:1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A. M. and Shevach, E. M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human interleukin- $\gamma$ , Schreiber, R. D. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L. S. and Lipsky, P. E. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad.

- Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6--Nordan, R. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Aced. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11--Bennett, F.,
- 5 Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9--Ciarletta, A., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.
- 10 Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W Strober, Pub. Greene Publishing
- 15 Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

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#### 4.7.4 STEM CELL GROWTH FACTOR ACTIVITY

- A polypeptide of the present invention may exhibit stem cell growth factor activity and be involved in the proliferation, differentiation and survival of pluripotent and totipotent stem cells including primordial germ cells, embryonic stem cells,
- 25 hematopoietic stem cells and/or germ line stem cells. Administration of the polypeptide of the invention to stem cells *in vivo* or *ex vivo* is expected to maintain and expand cell populations in a totipotent or pluripotent state which would be useful for re-engineering damaged or diseased tissues, transplantation, manufacture of bio-pharmaceuticals and the development of bio-sensors. The ability to produce large
- 30 quantities of human cells has important working applications for the production of

human proteins which currently must be obtained from non-human sources or donors, implantation of cells to treat diseases such as Parkinson's, Alzheimer's and other neurodegenerative diseases; tissues for grafting such as bone marrow, skin, cartilage, tendons, bone, muscle (including cardiac muscle), blood vessels, cornea, neural cells, gastrointestinal cells and others; and organs for transplantation such as kidney, liver, pancreas (including islet cells), heart and lung.

It is contemplated that multiple different exogenous growth factors and/or cytokines may be administered in combination with the polypeptide of the invention to achieve the desired effect, including any of the growth factors listed herein, other stem cell maintenance factors, and specifically including stem cell factor (SCF), leukemia inhibitory factor (LIF), Flt-3 ligand (Flt-3L), any of the interleukins, recombinant soluble IL-6 receptor fused to IL-6, macrophage inflammatory protein 1-alpha (MIP-1-alpha), G-CSF, GM-CSF, thrombopoietin (TPO), platelet factor 4 (PF-4), platelet-derived growth factor (PDGF), neural growth factors and basic fibroblast growth factor (bFGF).

Since totipotent stem cells can give rise to virtually any mature cell type, expansion of these cells in culture will facilitate the production of large quantities of mature cells. Techniques for culturing stem cells are known in the art and administration of polypeptides of the invention, optionally with other growth factors and/or cytokines, is expected to enhance the survival and proliferation of the stem cell populations. This can be accomplished by direct administration of the polypeptide of the invention to the culture medium. Alternatively, stroma cells transfected with a polynucleotide that encodes for the polypeptide of the invention can be used as a feeder layer for the stem cell populations in culture or in vivo. Stromal support cells for feeder layers may include embryonic bone marrow fibroblasts, bone marrow stromal cells, fetal liver cells, or cultured embryonic fibroblasts (see U.S. Patent No. 5,690,926).

Stem cells themselves can be transfected with a polynucleotide of the invention to induce autocrine expression of the polypeptide of the invention. This will allow for generation of undifferentiated totipotent/pluripotent stem cell lines that are useful

as is or that can then be differentiated into the desired mature cell types. These stable cell lines can also serve as a source of undifferentiated totipotent/pluripotent mRNA to create cDNA libraries and templates for polymerase chain reaction experiments. These studies would allow for the isolation and identification of differentially expressed genes in stem cell populations that regulate stem cell proliferation and/or maintenance.

Expansion and maintenance of totipotent stem cell populations will be useful in the treatment of many pathological conditions. For example, polypeptides of the present invention may be used to manipulate stem cells in culture to give rise to neuroepithelial cells that can be used to augment or replace cells damaged by illness, autoimmune disease, accidental damage or genetic disorders. The polypeptide of the invention may be useful for inducing the proliferation of neural cells and for the regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders which involve degeneration, death or trauma to neural cells or nerve tissue. In addition, the expanded stem cell populations can also be genetically altered for gene therapy purposes and to decrease host rejection of replacement tissues after grafting or implantation.

Expression of the polypeptide of the invention and its effect on stem cells can also be manipulated to achieve controlled differentiation of the stem cells into more differentiated cell types. A broadly applicable method of obtaining pure populations of a specific differentiated cell type from undifferentiated stem cell populations involves the use of a cell-type specific promoter driving a selectable marker. The selectable marker allows only cells of the desired type to survive. For example, stem cells can be induced to differentiate into cardiomyocytes (Wobus et al., *Differentiation*, 48: 173-182, (1991); Klug et al., *J. Clin. Invest.*, 98(1): 216-224, (1998)) or skeletal muscle cells (Browder, L. W. In: *Principles of Tissue Engineering* eds. Lanza et al., Academic Press (1997)). Alternatively, directed differentiation of stem cells can be accomplished by culturing the stem cells in the presence of a differentiation factor such as retinoic acid and an antagonist of the polypeptide of the invention which would

inhibit the effects of endogenous stem cell factor activity and allow differentiation to proceed.

*In vitro* cultures of stem cells can be used to determine if the polypeptide of the invention exhibits stem cell growth factor activity. Stem cells are isolated from any one of various cell sources (including hematopoietic stem cells and embryonic stem cells) and cultured on a feeder layer, as described by Thompson et al. Proc. Natl. Acad. Sci, U.S.A., 92: 7844-7848 (1995), in the presence of the polypeptide of the invention alone or in combination with other growth factors or cytokines. The ability of the polypeptide of the invention to induce stem cells proliferation is determined by colony formation on semi-solid support e.g. as described by Bernstein et al., Blood, 77: 2316-2321 (1991).

#### 4.7.5 HEMATOPOIESIS REGULATING ACTIVITY

A polypeptide of the present invention may be involved in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell disorders. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with

transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

Therapeutic compositions of the invention can be used in the following:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M. G. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, N.Y. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I. K. and Briddell, R. A. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, N.Y. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R. E. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, N.Y. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, N.Y. 1994; Long term culture initiating cell assay, Sutherland, H. J. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, N.Y. 1994.

#### 4.7.6 TISSUE GROWTH ACTIVITY

A polypeptide of the present invention also may be involved in bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as in wound healing and tissue repair and replacement, and in healing of burns, incisions and ulcers.

5 A polypeptide of the present invention which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Compositions of a polypeptide, antibody, binding partner, or other modulator of the invention may have prophylactic use in closed as well as open fracture reduction and  
10 also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A polypeptide of this invention may also be involved in attracting bone-forming cells, stimulating growth of bone-forming cells, or inducing differentiation of  
15 progenitors of bone-forming cells. Treatment of osteoporosis, osteoarthritis, bone degenerative disorders, or periodontal disease, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes may also be possible using the composition of the invention.

20 Another category of tissue regeneration activity that may involve the polypeptide of the present invention is tendon/ligament formation. Induction of tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a  
25 preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of  
30 congenital, trauma induced, or other tendon or ligament defects of other origin, and is

also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The compositions of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a composition may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a composition of the invention.

Compositions of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

Compositions of the present invention may also be involved in the generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation



of fibrotic scarring may allow normal tissue to regenerate. A polypeptide of the present invention may also exhibit angiogenic activity.

A composition of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various  
5 tissues, and conditions resulting from systemic cytokine damage.

A composition of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Therapeutic compositions of the invention can be used in the following:

10 Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

15 Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, H. I. and Rovee, D. T., eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

#### **4.7.7 IMMUNE STIMULATING OR SUPPRESSING ACTIVITY**

20 A polypeptide of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A polynucleotide of the invention can encode a polypeptide exhibiting such activities. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g.,  
25 in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable  
30 using a protein of the present invention, including infections by HIV, hepatitis viruses,

herpes viruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, proteins of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

5           Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease.

10       Such a protein (or antagonists thereof, including antibodies) of the present invention may also to be useful in the treatment of allergic reactions and conditions (*e.g.*, anaphylaxis, serum sickness, drug reactions, food allergies, insect venom allergies, mastocytosis, allergic rhinitis, hypersensitivity pneumonitis, urticaria, angioedema, eczema, atopic dermatitis, allergic contact dermatitis, erythema multiforme, Stevens-  
15       Johnson syndrome, allergic conjunctivitis, atopic keratoconjunctivitis, venereal keratoconjunctivitis, giant papillary conjunctivitis and contact allergies), such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein (or antagonists thereof) of the present invention. The  
20       therapeutic effects of the polypeptides or antagonists thereof on allergic reactions can be evaluated by in vivo animals models such as the cumulative contact enhancement test (Lastbom et al., Toxicology 125: 59-66, 1998), skin prick test (Hoffmann et al., Allergy 54: 446-54, 1999), guinea pig skin sensitization test (Vohr et al., Arch. Toxicol. 73: 501-9), and murine local lymph node assay (Kimber et al., J. Toxicol. Environ. Health 53: 563-79).  
25       

          Using the proteins of the invention it may also be possible to modulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited  
30       by suppressing T cell responses or by inducing specific tolerance in T cells, or both.

Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a therapeutic composition of the invention may prevent cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, a lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular therapeutic compositions in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York,

1989, pp. 846-847) can be used to determine the effect of therapeutic compositions of the invention on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block stimulation of T cells can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (e.g., a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response may be useful in cases of viral infection, including systemic viral diseases such as influenza, the common cold, and encephalitis.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient,

transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

A polypeptide of the present invention may provide the necessary stimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient mounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I alpha chain protein and  $\beta_2$  microglobulin protein or an MHC class II alpha chain protein and an MHC class II beta chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J.

Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., I. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bowman et al., J. Virology 61:1992-1998; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

5            Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J. J. and Brunswick, M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, 10            Toronto. 1994.

              Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, 15            A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

20            Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 25            182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

              Assays for lymphocyte survival/apoptosis (which will identify, among others, 30            proteins that prevent apoptosis after superantigen induction and proteins that regulate

lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al.,  
5 Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al.,  
10 Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

#### 4.7.8 ACTIVIN/INHIBIN ACTIVITY

A polypeptide of the present invention may also exhibit activin- or  
15 inhibin-related activities. A polynucleotide of the invention may encode a polypeptide exhibiting such characteristics. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a polypeptide of the present invention, alone or in heterodimers with a member of the  
20 inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the polypeptide of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin group, may be useful as a fertility  
25 inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, U.S. Pat. No. 4,798,885. A polypeptide of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as, but not limited to, cows, sheep and pigs.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods.

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

#### 4.7.9 CHEMOTACTIC/CHEMOKINETIC ACTIVITY

A polypeptide of the present invention may be involved in chemotactic or chemokinetic activity for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Chemotactic and chemokinetic receptor activation can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic compositions (e.g. proteins, antibodies, binding partners, or modulators of the invention) provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

Therapeutic compositions of the invention can be used in the following:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for



movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Marguiles, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

#### **4.7.10 HEMOSTATIC AND THROMBOLYTIC ACTIVITY**

A polypeptide of the invention may also be involved in hemostatis or thrombolysis or thrombosis. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Compositions may be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A composition of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

Therapeutic compositions of the invention can be used in the following:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-164, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

#### **4.7.11 CANCER DIAGNOSIS AND THERAPY**

Polypeptides of the invention may be involved in cancer cell generation, proliferation or metastasis. Detection of the presence or amount of polynucleotides or polypeptides of the invention may be useful for the diagnosis and/or prognosis of one or more types of cancer. For example, the presence or increased expression of a polynucleotide/polypeptide of the invention may indicate a hereditary risk of cancer, a

precancerous condition, or an ongoing malignancy. Conversely, a defect in the gene or absence of the polypeptide may be associated with a cancer condition. Identification of single nucleotide polymorphisms associated with cancer or a predisposition to cancer may also be useful for diagnosis or prognosis.

5 Cancer treatments promote tumor regression by inhibiting tumor cell proliferation, inhibiting angiogenesis (growth of new blood vessels that is necessary to support tumor growth) and/or prohibiting metastasis by reducing tumor cell motility or invasiveness. Therapeutic compositions of the invention may be effective in adult and pediatric oncology including in solid phase tumors/malignancies, locally advanced  
10 tumors, human soft tissue sarcomas, metastatic cancer, including lymphatic metastases, blood cell malignancies including multiple myeloma, acute and chronic leukemias, and lymphomas, head and neck cancers including mouth cancer, larynx cancer and thyroid cancer, lung cancers including small cell carcinoma and non-small cell cancers, breast cancers including small cell carcinoma and ductal carcinoma, gastrointestinal cancers  
15 including esophageal cancer, stomach cancer, colon cancer, colorectal cancer and polyps associated with colorectal neoplasia, pancreatic cancers, liver cancer, urologic cancers including bladder cancer and prostate cancer, malignancies of the female genital tract including ovarian carcinoma, uterine (including endometrial) cancers, and solid tumor in the ovarian follicle, kidney cancers including renal cell carcinoma, brain  
20 cancers including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous system, bone cancers including osteomas, skin cancers including malignant melanoma, tumor progression of human skin keratinocytes, squamous cell carcinoma, basal cell carcinoma, hemangiopericytoma and Kaposi's sarcoma.

25 Polypeptides, polynucleotides, or modulators of polypeptides of the invention (including inhibitors and stimulators of the biological activity of the polypeptide of the invention) may be administered to treat cancer. Therapeutic compositions can be administered in therapeutically effective dosages alone or in combination with adjuvant cancer therapy such as surgery, chemotherapy, radiotherapy, thermotherapy, and laser  
30 therapy, and may provide a beneficial effect, e.g. reducing tumor size, slowing rate of

tumor growth, inhibiting metastasis, or otherwise improving overall clinical condition, without necessarily eradicating the cancer.

The composition can also be administered in therapeutically effective amounts as a portion of an anti-cancer cocktail. An anti-cancer cocktail is a mixture of the

5 polypeptide or modulator of the invention with one or more anti-cancer drugs in addition to a pharmaceutically acceptable carrier for delivery. The use of anti-cancer cocktails as a cancer treatment is routine. Anti-cancer drugs that are well known in the art and can be used as a treatment in combination with the polypeptide or modulator of the invention include: Actinomycin D, Aminoglutethimide, Asparaginase, Bleomycin, 10 Busulfan, Carboplatin, Carmustine, Chlorambucil, Cisplatin (cis-DDP), Cyclophosphamide, Cytarabine HCl (Cytosine arabinoside), Dacarbazine, Dactinomycin, Daunorubicin HCl, Doxorubicin HCl, Estramustine phosphate sodium, Etoposide (V16-213), Floxuridine, 5-Fluorouracil (5-Fu), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alpha-2a, Interferon Alpha-2b, Leuprolide 15 acetate (LHRH-releasing factor analog), Lomustine, Mechlorethamine HCl (nitrogen mustard), Melphalan, Mercaptopurine, Mesna, Methotrexate (MTX), Mitomycin, Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Vincristine sulfate, Amsacrine, Azacitidine, Hexamethylmelamine, Interleukin-2, Mitoguazone, 20 Pentostatin, Semustine, Teniposide, and Vindesine sulfate.

In addition, therapeutic compositions of the invention may be used for prophylactic treatment of cancer. There are hereditary conditions and/or environmental situations (e.g. exposure to carcinogens) known in the art that predispose an individual to developing cancers. Under these circumstances, it may be beneficial to treat these 25 individuals with therapeutically effective doses of the polypeptide of the invention to reduce the risk of developing cancers.

*In vitro* models can be used to determine the effective doses of the polypeptide of the invention as a potential cancer treatment. These *in vitro* models include proliferation assays of cultured tumor cells, growth of cultured tumor cells in soft agar 30 (see Freshney, (1987) Culture of Animal Cells: A Manual of Basic Technique, Wiley-

Liss, New York, NY Ch 18 and Ch 21), tumor systems in nude mice as described in Giovanella et al., J. Natl. Can. Inst., 52: 921-30 (1974), mobility and invasive potential of tumor cells in Boyden Chamber assays as described in Pilkington et al., Anticancer Res., 17: 4107-9 (1997), and angiogenesis assays such as induction of vascularization of the chick chorioallantoic membrane or induction of vascular endothelial cell migration as described in Ribatta et al., Intl. J. Dev. Biol., 40: 1189-97 (1999) and Li et al., Clin. Exp. Metastasis, 17:423-9 (1999), respectively. Suitable tumor cells lines are available, e.g. from American Type Tissue Culture Collection catalogs.

#### 4.7.12 RECEPTOR/LIGAND ACTIVITY

A polypeptide of the present invention may also demonstrate activity as receptor, receptor ligand or inhibitor or agonist of receptor/ligand interactions. A polynucleotide of the invention can encode a polypeptide exhibiting such characteristics. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses. Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley- Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1- 7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA

84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

By way of example, the polypeptides of the invention may be used as a receptor for a ligand(s) thereby transmitting the biological activity of that ligand(s). Ligands may be identified through binding assays, affinity chromatography, dihybrid screening assays, BIAcore assays, gel overlay assays, or other methods known in the art.

Studies characterizing drugs or proteins as agonist or antagonist or partial agonists or a partial antagonist require the use of other proteins as competing ligands. The polypeptides of the present invention or ligand(s) thereof may be labeled by being coupled to radioisotopes, colorimetric molecules or a toxin molecules by conventional methods. ("Guide to Protein Purification" Murray P. Deutscher (ed) Methods in Enzymology Vol. 182 (1990) Academic Press, Inc. San Diego). Examples of radioisotopes include, but are not limited to, tritium and carbon-14 . Examples of colorimetric molecules include, but are not limited to, fluorescent molecules such as fluorescamine, or rhodamine or other colorimetric molecules. Examples of toxins include, but are not limited, to ricin.

#### 4.7.13 DRUG SCREENING

This invention is particularly useful for screening chemical compounds by using the novel polypeptides or binding fragments thereof in any of a variety of drug screening techniques. The polypeptides or fragments employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or a fragment thereof. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between polypeptides of the invention or fragments and the agent being

tested or examine the diminution in complex formation between the novel polypeptides and an appropriate cell line, which are well known in the art.

Sources for test compounds that may be screened for ability to bind to or modulate (i.e., increase or decrease) the activity of polypeptides of the invention  
5 include (1) inorganic and organic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of either random or mimetic peptides, oligonucleotides or organic molecules.

Chemical libraries may be readily synthesized or purchased from a number of commercial sources, and may include structural analogs of known compounds or  
10 compounds that are identified as "hits" or "leads" via natural product screening.

The sources of natural product libraries are microorganisms (including bacteria and fungi), animals, plants or other vegetation, or marine organisms, and libraries of mixtures for screening may be created by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of the organisms  
15 themselves. Natural product libraries include polyketides, non-ribosomal peptides, and (non-naturally occurring) variants thereof. For a review, see *Science* 282:63-68 (1998).

Combinatorial libraries are composed of large numbers of peptides, oligonucleotides or organic compounds and can be readily prepared by traditional  
20 automated synthesis methods, PCR, cloning or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, *Curr. Opin. Biotechnol.* 8:701-  
25 707 (1997). For reviews and examples of peptidomimetic libraries, see Al-Obeidi et al., *Mol. Biotechnol.*, 9(3):205-23 (1998); Hruby et al., *Curr Opin Chem Biol*, 1(1):114-19 (1997); Dorner et al., *Bioorg Med Chem*, 4(5):709-15 (1996) (alkylated dipeptides).

Identification of modulators through use of the various libraries described herein  
30 permits modification of the candidate "hit" (or "lead") to optimize the capacity of the

“hit” to bind a polypeptide of the invention. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

The binding molecules thus identified may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells such as radioisotopes. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for a polypeptide of the invention. Alternatively, the binding molecules may be complexed with imaging agents for targeting and imaging purposes.

#### 4.7.14 ASSAY FOR RECEPTOR ACTIVITY

The invention also provides methods to detect specific binding of a polypeptide e.g. a ligand or a receptor. The art provides numerous assays particularly useful for identifying previously unknown binding partners for receptor polypeptides of the invention. For example, expression cloning using mammalian or bacterial cells, or dihybrid screening assays can be used to identify polynucleotides encoding binding partners. As another example, affinity chromatography with the appropriate immobilized polypeptide of the invention can be used to isolate polypeptides that recognize and bind polypeptides of the invention. There are a number of different libraries used for the identification of compounds, and in particular small molecules, that modulate (*i.e.*, increase or decrease) biological activity of a polypeptide of the invention. Ligands for receptor polypeptides of the invention can also be identified by adding exogenous ligands, or cocktails of ligands to two cells populations that are genetically identical except for the expression of the receptor of the invention: one cell population expresses the receptor of the invention whereas the other does not. The response of the two cell populations to the addition of ligands(s) are then compared. Alternatively, an expression library can be co-expressed with the polypeptide of the invention in cells and assayed for an autocrine response to identify potential ligand(s).

As still another example, BIAcore assays, gel overlay assays, or other methods known in the art can be used to identify binding partner polypeptides, including, (1) organic and inorganic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules.

5           The role of downstream intracellular signaling molecules in the signaling cascade of the polypeptide of the invention can be determined. For example, a chimeric protein in which the cytoplasmic domain of the polypeptide of the invention is fused to the extracellular portion of a protein, whose ligand has been identified, is produced in a host cell. The cell is then incubated with the ligand specific for the extracellular portion  
10 of the chimeric protein, thereby activating the chimeric receptor. Known downstream proteins involved in intracellular signaling can then be assayed for expected modifications i.e. phosphorylation. Other methods known to those in the art can also be used to identify signaling molecules involved in receptor activity.

#### 15           **4.7.15 ANTI-INFLAMMATORY ACTIVITY**

          Compositions of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting  
20 chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Compositions with such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation intimation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion  
25 injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Compositions of the invention may also be useful to treat anaphylaxis and  
30 hypersensitivity to an antigenic substance or material. Compositions of this invention



may be utilized to prevent or treat conditions such as, but not limited to, sepsis, acute pancreatitis, endotoxin shock, cytokine induced shock, rheumatoid arthritis, chronic inflammatory arthritis, pancreatic cell damage from diabetes mellitus type 1, graft versus host disease, inflammatory bowel disease, inflammation associated with pulmonary disease, other autoimmune disease or inflammatory disease, an antiproliferative agent such as for acute or chronic myelogenous leukemia or in the prevention of premature labor secondary to intrauterine infections.

#### **4.7.16 LEUKEMIAS**

Leukemias and related disorders may be treated or prevented by administration of a therapeutic that promotes or inhibits function of the polynucleotides and/or polypeptides of the invention. Such leukemias and related disorders include but are not limited to acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia, chronic leukemia, chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia (for a review of such disorders, see Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia).

#### **4.7.17 NERVOUS SYSTEM DISORDERS**

Nervous system disorders, involving cell types which can be tested for efficacy of intervention with compounds that modulate the activity of the polynucleotides and/or polypeptides of the invention, and which can be treated upon thus observing an indication of therapeutic utility, include but are not limited to nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the invention include but are not limited to the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems:

(i) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries;

5 (ii) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia;

(iii) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or  
10 with Lyme disease, tuberculosis, syphilis;

(iv) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis;

15 (v) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration;

20 (vi) neurological lesions associated with systemic diseases including but not limited to diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis;

(vii) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and

25 (viii) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including but not limited to multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

Therapeutics which are useful according to the invention for treatment of a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, therapeutics which elicit any of the following effects may be useful according to the invention:

- (i) increased survival time of neurons in culture;
- (ii) increased sprouting of neurons in culture or *in vivo*;
- (iii) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or
- (iv) decreased symptoms of neuron dysfunction *in vivo*.

Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may be measured by the method set forth in Arakawa et al. (1990, J. Neurosci. 10:3507-3515); increased sprouting of neurons may be detected by methods set forth in Pestronk et al. (1980, Exp. Neurol. 70:65-82) or Brown et al. (1981, Ann. Rev. Neurosci. 4:17-42); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, *etc.*, depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, *e.g.*, weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include but are not limited to disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including but not limited to progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

#### 4.7.18 OTHER ACTIVITIES

A polypeptide of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, co-factors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

#### 4.7.19 IDENTIFICATION OF POLYMORPHISMS

The demonstration of polymorphisms makes possible the identification of such polymorphisms in human subjects and the pharmacogenetic use of this information for diagnosis and treatment. Such polymorphisms may be associated with, e.g., differential predisposition or susceptibility to various disease states (such as disorders involving inflammation or immune response) or a differential response to drug administration,

and this genetic information can be used to tailor preventive or therapeutic treatment appropriately. For example, the existence of a polymorphism associated with a predisposition to inflammation or autoimmune disease makes possible the diagnosis of this condition in humans by identifying the presence of the polymorphism.

5 Polymorphisms can be identified in a variety of ways known in the art which all generally involve obtaining a sample from a patient, analyzing DNA from the sample, optionally involving isolation or amplification of the DNA, and identifying the presence of the polymorphism in the DNA. For example, PCR may be used to amplify an appropriate fragment of genomic DNA which may then be sequenced. Alternatively,  
10 the DNA may be subjected to allele-specific oligonucleotide hybridization (in which appropriate oligonucleotides are hybridized to the DNA under conditions permitting detection of a single base mismatch) or to a single nucleotide extension assay (in which an oligonucleotide that hybridizes immediately adjacent to the position of the polymorphism is extended with one or more labeled nucleotides). In addition,  
15 traditional restriction fragment length polymorphism analysis (using restriction enzymes that provide differential digestion of the genomic DNA depending on the presence or absence of the polymorphism) may be performed. Arrays with nucleotide sequences of the present invention can be used to detect polymorphisms. The array can comprise modified nucleotide sequences of the present invention in order to detect the nucleotide  
20 sequences of the present invention. In the alternative, any one of the nucleotide sequences of the present invention can be placed on the array to detect changes from those sequences.

Alternatively a polymorphism resulting in a change in the amino acid sequence could also be detected by detecting a corresponding change in amino acid sequence of  
25 the protein, e.g., by an antibody specific to the variant sequence.

#### 4.7.20 ARTHRITIS AND INFLAMMATION

The immunosuppressive effects of the compositions of the invention against rheumatoid arthritis is determined in an experimental animal model system. The  
30 experimental model system is adjuvant induced arthritis in rats, and the protocol is

described by J. Holoshitz, et al., 1983, Science, 219:56, or by B. Waksman et al., 1963, Int. Arch. Allergy Appl. Immunol., 23:129. Induction of the disease can be caused by a single injection, generally intradermally, of a suspension of killed Mycobacterium tuberculosis in complete Freund's adjuvant (CFA). The route of injection can vary, but rats may be injected at the base of the tail with an adjuvant mixture. The polypeptide is administered in phosphate buffered solution (PBS) at a dose of about 1-5 mg/kg. The control consists of administering PBS only.

The procedure for testing the effects of the test compound would consist of intradermally injecting killed Mycobacterium tuberculosis in CFA followed by immediately administering the test compound and subsequent treatment every other day until day 24. At 14, 15, 18, 20, 22, and 24 days after injection of Mycobacterium CFA, an overall arthritis score may be obtained as described by J. Holoskitz above. An analysis of the data would reveal that the test compound would have a dramatic affect on the swelling of the joints as measured by a decrease of the arthritis score.

#### 4.8 THERAPEUTIC METHODS

The compositions (including polypeptide fragments, analogs, variants and antibodies or other binding partners or modulators including antisense polynucleotides) of the invention have numerous applications in a variety of therapeutic methods. Examples of therapeutic applications include, but are not limited to, those exemplified herein.

##### 4.8.1 EXAMPLE

One embodiment of the invention is the administration of an effective amount of the polypeptides or other composition of the invention to individuals affected by a disease or disorder that can be modulated by regulating the peptides of the invention. While the mode of administration is not particularly important, parenteral administration is preferred. An exemplary mode of administration is to deliver an intravenous bolus. The dosage of the polypeptides or other composition of the

invention will normally be determined by the prescribing physician. It is to be expected that the dosage will vary according to the age, weight, condition and response of the individual patient. Typically, the amount of polypeptide administered per dose will be in the range of about 0.01µg/kg to 100 mg/kg of body weight, with the preferred dose being about 0.1µg/kg to 10 mg/kg of patient body weight. For parenteral administration, polypeptides of the invention will be formulated in an injectable form combined with a pharmaceutically acceptable parenteral vehicle. Such vehicles are well known in the art and examples include water, saline, Ringer's solution, dextrose solution, and solutions consisting of small amounts of the human serum albumin. The vehicle may contain minor amounts of additives that maintain the isotonicity and stability of the polypeptide or other active ingredient. The preparation of such solutions is within the skill of the art.

#### **4.9 PHARMACEUTICAL FORMULATIONS AND ROUTES OF ADMINISTRATION**

A protein or other composition of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources and including antibodies and other binding partners of the polypeptides of the invention) may be administered to a patient in need, by itself, or in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s) at doses to treat or ameliorate a variety of disorders. Such a composition may optionally contain (in addition to protein or other active ingredient and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF,

Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the disease or disorder in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factors (TGF- $\alpha$  and TGF- $\beta$ ), insulin-like growth factor (IGF), as well as cytokines described herein.

The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or other active ingredient or complement its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein or other active ingredient of the invention, or to minimize side effects. Conversely, protein or other active ingredient of the present invention may be included in formulations of the particular clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent (such as IL-1Ra, IL-1 Hy1, IL-1 Hy2, anti-TNF, corticosteroids, immunosuppressive agents). A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

As an alternative to being included in a pharmaceutical composition of the invention including a first protein, a second protein or a therapeutic agent may be concurrently administered with the first protein (e.g., at the same time, or at differing times provided that therapeutic concentrations of the combination of agents is achieved at the treatment site). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition. A therapeutically effective dose further refers to that amount of the compound sufficient to result in amelioration of symptoms, e.g., treatment, healing, prevention or amelioration of the relevant medical



condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, a therapeutically effective dose refers to that ingredient alone. When applied to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein or other active ingredient of the present invention is administered to a mammal having a condition to be treated. Protein or other active ingredient of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein or other active ingredient of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein or other active ingredient of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

#### 4.9.1 ROUTES OF ADMINISTRATION

Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Administration of protein or other active ingredient of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or

cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection.

Intravenous administration to the patient is preferred.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a arthritic joints or in fibrotic tissue, often in a depot or sustained release formulation. In order to prevent the scarring process frequently occurring as complication of glaucoma surgery, the compounds may be administered topically, for example, as eye drops. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a specific antibody, targeting, for example, arthritic or fibrotic tissue. The liposomes will be targeted to and taken up selectively by the afflicted tissue.

The polypeptides of the invention are administered by any route that delivers an effective dosage to the desired site of action. The determination of a suitable route of administration and an effective dosage for a particular indication is within the level of skill in the art. Preferably for wound treatment, one administers the therapeutic compound directly to the site. Suitable dosage ranges for the polypeptides of the invention can be extrapolated from these dosages or from similar studies in appropriate animal models. Dosages can then be adjusted as necessary by the clinician to provide maximal therapeutic benefit.

#### 4.9.2 COMPOSITIONS/FORMULATIONS

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. These pharmaceutical compositions may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of protein or other active ingredient of the present

invention is administered orally, protein or other active ingredient of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein or other active ingredient of the present invention, and preferably from about 25 to 90% protein or other active ingredient of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein or other active ingredient of the present invention, and preferably from about 1 to 50% protein or other active ingredient of the present invention.

When a therapeutically effective amount of protein or other active ingredient of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein or other active ingredient of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein or other active ingredient solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein or other active ingredient of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art. For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For

transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art.

5 Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained from a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or  
10 dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as  
15 the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or  
20 pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in  
25 admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such

administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch. The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides. In addition to the formulations described

previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a co-solvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The co-solvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose. Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological

stability of the therapeutic reagent, additional strategies for protein or other active ingredient stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Many of the active ingredients of the invention may be provided as salts with pharmaceutically compatible counter ions. Such pharmaceutically acceptable base addition salts are those salts which retain the biological effectiveness and properties of the free acids and which are obtained by reaction with inorganic or organic bases such as sodium hydroxide, magnesium hydroxide, ammonia, trialkylamine, dialkylamine, monoalkylamine, dibasic amino acids, sodium acetate, potassium benzoate, triethanol amine and the like.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) or other active ingredient(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without

limitation, monoglycerides, diglycerides, sulfatides, lysolecithins, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent Nos. 4,235,871; 4,501,728; 4,837,028; and 4,737,323, all of which are incorporated herein by  
5 reference.

The amount of protein or other active ingredient of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of  
10 protein or other active ingredient of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein or other active ingredient of the present invention and observe the patient's response. Larger doses of protein or other active ingredient of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and  
15 at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01  $\mu$ g to about 100 mg (preferably about 0.1  $\mu$ g to about 10 mg, more preferably about 0.1  $\mu$ g to about 1 mg) of protein or other active ingredient of the present invention per kg body weight. For compositions of the present invention which  
20 are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for  
25 delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein or other active ingredient of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the  
30 invention. Preferably for bone and/or cartilage formation, the composition would



include a matrix capable of delivering the protein-containing or other active ingredient-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalcium phosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability. Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent

useful herein is 0.5-20 wt %, preferably 1-10 wt % based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby  
5 providing the protein the opportunity to assist the osteogenic activity of the progenitor cells. In further compositions, proteins or other active ingredients of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming  
10 growth factors (TGF- $\alpha$  and TGF- $\beta$ ), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins or other active ingredients of the present invention. The dosage regimen of a protein-containing pharmaceutical  
15 composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, *e.g.*, amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (*e.g.*, bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other  
20 clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays,  
25 histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either in vivo or ex vivo into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including,  
30 without limitation, in the form of viral vectors or naked DNA). Cells may also be

cultured ex vivo in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced in vivo for therapeutic purposes.

#### 5           **4.9.3 EFFECTIVE DOSAGE**

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing  
10 symptoms of the subject being treated. Determination of the effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from appropriate in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating  
15 concentration range that can be used to more accurately determine useful doses in humans. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC<sub>50</sub> as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of the protein's biological activity). Such information can be used to more accurately  
20 determine useful doses in humans.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for  
25 determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD<sub>50</sub> and ED<sub>50</sub>. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in  
30 formulating a range of dosage for use in human. The dosage of such compounds lies

preferably within a range of circulating concentrations that include the ED<sub>50</sub> with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. See, *e.g.*, Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1. Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the desired effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

An exemplary dosage regimen for polypeptides or other compositions of the invention will be in the range of about 0.01 µg/kg to 100 mg/kg of body weight daily, with the preferred dose being about 0.1 µg/kg to 25 mg/kg of patient body weight daily, varying in adults and children. Dosing may be once daily, or equivalent doses may be delivered at longer or shorter intervals.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's age and weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

#### 4.9.4 PACKAGING

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

#### 5    4.10 ANTIBODIES

Another aspect of the invention is an antibody that specifically binds the polypeptide of the invention. Such antibodies include monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, including compounds which include CDR and/or antigen-binding sequences, which specifically recognize a polypeptide of the invention. Preferred antibodies of the invention are human antibodies which are produced and identified according to methods described in WO93/11236, published June 20, 1993, which is incorporated herein by reference in its entirety. Antibody fragments, including Fab, Fab', F(ab')<sub>2</sub>, and F<sub>v</sub>, are also provided by the invention. The term "specific for" indicates that the variable regions of the antibodies of the invention recognize and bind polypeptides of the invention exclusively (*i.e.*, able to distinguish the polypeptide of the invention from other similar polypeptides despite sequence identity, homology, or similarity found in the family of polypeptides), but may also interact with other proteins (for example, *S. aureus* protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow et al. (Eds), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor , NY (1988), Chapter 6. Antibodies that recognize and bind fragments of the polypeptides of the invention are also contemplated, provided that the antibodies are first and foremost specific for, as defined above, full length polypeptides of the invention. As with antibodies that are specific for full length polypeptides of the invention, antibodies of the invention that recognize fragments are those which can

distinguish polypeptides from the same family of polypeptides despite inherent sequence identity, homology, or similarity found in the family of proteins. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

5 Non-human antibodies may be humanized by any methods known in the art. In one method, the non-human CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.

10 Antibodies of the invention are useful for, for example, therapeutic purposes (by modulating activity of a polypeptide of the invention), diagnostic purposes to detect or quantitate a polypeptide of the invention, as well as purification of a polypeptide of the invention. Kits comprising an antibody of the invention for any of the purposes described herein are also comprehended. In general, a kit of the invention also includes a control antigen for which the antibody is immunospecific. The invention further  
15 provides a hybridoma that produces an antibody according to the invention. Antibodies of the invention are useful for detection and/or purification of the polypeptides of the invention.

Polypeptides of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such  
20 antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R. P. Merrifield, J. Amer. Chem. Soc. 85, 2149-2154 (1963); J. L.  
25 Krstenansky, et al., FEBS Lett. 211, 10 (1987).

Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where  
30 abnormal expression of the protein is involved. In the case of cancerous cells or

leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein. In general, techniques for preparing polyclonal and monoclonal antibodies as well as hybridomas capable of producing the desired antibody are well known in the art (Campbell, A.M., Monoclonal Antibodies Technology: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1984); St. Groth et al., J. Immunol. 35:1-21 (1990); Kohler and Milstein, Nature 256:495-497 (1975)), the trioma technique, the human B-cell hybridoma technique (Kozbor et al., Immunology Today 4:72 (1983); Cole et al., in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. (1985), pp. 77-96).

Any animal (mouse, rabbit, *etc.*) which is known to produce antibodies can be immunized with a peptide or polypeptide of the invention. Methods for immunization are well known in the art. Such methods include subcutaneous or intraperitoneal injection of the polypeptide. One skilled in the art will recognize that the amount of the protein encoded by the ORF of the present invention used for immunization will vary based on the animal which is immunized, the antigenicity of the peptide and the site of injection. The protein that is used as an immunogen may be modified or administered in an adjuvant in order to increase the protein's antigenicity. Methods of increasing the antigenicity of a protein are well known in the art and include, but are not limited to, coupling the antigen with a heterologous protein (such as globulin or  $\alpha$ -galactosidase) or through the inclusion of an adjuvant during immunization.

For monoclonal antibodies, spleen cells from the immunized animals are removed, fused with myeloma cells, such as SP2/0-Ag14 myeloma cells, and allowed to become monoclonal antibody producing hybridoma cells. Any one of a number of methods well known in the art can be used to identify the hybridoma cell which produces an antibody with the desired characteristics. These include screening the hybridomas with an ELISA assay, Western blot analysis, or radioimmunoassay (Lutz et al., Exp. Cell Research. 175:109-124 (1988)). Hybridomas secreting the desired antibodies are cloned and the class and subclass is determined using procedures known

in the art (Campbell, A.M., Monoclonal Antibody Technology: Laboratory  
Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers,  
Amsterdam, The Netherlands (1984)). Techniques described for the production of  
single chain antibodies (U.S. Patent 4,946,778) can be adapted to produce single chain  
5 antibodies to proteins of the present invention.

For polyclonal antibodies, antibody-containing antiserum is isolated from the  
immunized animal and is screened for the presence of antibodies with the desired  
specificity using one of the above-described procedures. The present invention further  
provides the above-described antibodies in delectably labeled form. Antibodies can be  
10 delectably labeled through the use of radioisotopes, affinity labels (such as biotin,  
avidin, etc.), enzymatic labels (such as horseradish peroxidase, alkaline phosphatase,  
etc.) fluorescent labels (such as FITC or rhodamine, etc.), paramagnetic atoms, etc.  
Procedures for accomplishing such labeling are well-known in the art, for example, see  
(Sternberger, L.A. et al., J. Histochem. Cytochem. 18:315 (1970); Bayer, E.A. et al.,  
15 Meth. Enzym. 62:308 (1979); Engval, E. et al., Immunol. 109:129 (1972); Goding,  
J.W. J. Immunol. Meth. 13:215 (1976)).

The labeled antibodies of the present invention can be used for *in vitro*, *in vivo*,  
and *in situ* assays to identify cells or tissues in which a fragment of the polypeptide of  
interest is expressed. The antibodies may also be used directly in therapies or other  
20 diagnostics. The present invention further provides the above-described antibodies  
immobilized on a solid support. Examples of such solid supports include plastics such  
as polycarbonate, complex carbohydrates such as agarose and Sepharose®, acrylic  
resins and such as polyacrylamide and latex beads. Techniques for coupling antibodies  
to such solid supports are well known in the art (Weir, D.M. et al., "Handbook of  
25 Experimental Immunology" 4th Ed., Blackwell Scientific Publications, Oxford,  
England, Chapter 10 (1986); Jacoby, W.D. et al., Meth. Enzym. 34 Academic Press,  
N.Y. (1974)). The immobilized antibodies of the present invention can be used for *in*  
*vitro*, *in vivo*, and *in situ* assays as well as for immuno-affinity purification of the  
proteins of the present invention.



#### 4.11 COMPUTER READABLE SEQUENCES

In one application of this embodiment, a nucleotide sequence of the present invention can be recorded on computer readable media. As used herein, "computer readable media" refers to any medium which can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled artisan can readily appreciate how any of the presently known computer readable mediums can be used to create a manufacture comprising computer readable medium having recorded thereon a nucleotide sequence of the present invention. As used herein, "recorded" refers to a process for storing information on computer readable medium. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising the nucleotide sequence information of the present invention.

A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon a nucleotide sequence of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the nucleotide sequence information of the present invention on computer readable medium. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and Microsoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of data processor structuring formats (*e.g.* text file or database) in order to obtain computer readable medium having recorded thereon the nucleotide sequence information of the present invention.

By providing any of the nucleotide sequences SEQ ID NOs: 1 - 164 or a representative fragment thereof; or a nucleotide sequence at least 95% identical to any

of the nucleotide sequences of the SEQ ID NOs: 1 - 164 in computer readable form, a skilled artisan can routinely access the sequence information for a variety of purposes. Computer software is publicly available which allows a skilled artisan to access sequence information provided in a computer readable medium. The examples which follow demonstrate how software which implements the BLAST (Altschul et al., J. Mol. Biol. 215:403-410 (1990)) and BLAZE (Brutlag et al., Comp. Chem. 17:203-207 (1993)) search algorithms on a Sybase system is used to identify open reading frames (ORFs) within a nucleic acid sequence. Such ORFs may be protein encoding fragments and may be useful in producing commercially important proteins such as enzymes used in fermentation reactions and in the production of commercially useful metabolites.

As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the nucleotide sequence information of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate that any one of the currently available computer-based systems are suitable for use in the present invention. As stated above, the computer-based systems of the present invention comprise a data storage means having stored therein a nucleotide sequence of the present invention and the necessary hardware means and software means for supporting and implementing a search means. As used herein, "data storage means" refers to memory which can store nucleotide sequence information of the present invention, or a memory access means which can access manufactures having recorded thereon the nucleotide sequence information of the present invention.

As used herein, "search means" refers to one or more programs which are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of a known sequence which match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting

search means are and can be used in the computer-based systems of the present invention. Examples of such software includes, but is not limited to, Smith-Waterman, MacPattern (EMBL), BLASTN and BLASTA (NPOLYPEPTIDEIA). A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting homology searches can be adapted for use in the present computer-based systems. As used herein, a "target sequence" can be any nucleic acid or amino acid sequence of six or more nucleotides or two or more amino acids. A skilled artisan can readily recognize that the longer a target sequence is, the less likely a target sequence will be present as a random occurrence in the database. The most preferred sequence length of a target sequence is from about 10 to 300 amino acids, more preferably from about 30 to 100 nucleotide residues. However, it is well recognized that searches for commercially important fragments, such as sequence fragments involved in gene expression and protein processing, may be of shorter length.

As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration which is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzyme active sites and signal sequences. Nucleic acid target motifs include, but are not limited to, promoter sequences, hairpin structures and inducible expression elements (protein binding sequences).

#### 4.12 TRIPLE HELIX FORMATION

In addition, the fragments of the present invention, as broadly described, can be used to control gene expression through triple helix formation or antisense DNA or RNA, both of which methods are based on the binding of a polynucleotide sequence to DNA or RNA. Polynucleotides suitable for use in these methods are preferably 20 to 40 bases in length and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 15241:456 (1988); and Dervan et al., Science 251:1360 (1991))

or to the mRNA itself (antisense - Olmno, J. Neurochem. 56:560 (1991);  
Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca  
Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA  
transcription from DNA, while antisense RNA hybridization blocks translation of an  
5 mRNA molecule into polypeptide. Both techniques have been demonstrated to be  
effective in model systems. Information contained in the sequences of the present  
invention is necessary for the design of an antisense or triple helix oligonucleotide.

#### 4.13 DIAGNOSTIC ASSAYS AND KITS

10 The present invention further provides methods to identify the presence or  
expression of one of the ORFs of the present invention, or homolog thereof, in a test  
sample, using a nucleic acid probe or antibodies of the present invention, optionally  
conjugated or otherwise associated with a suitable label.

15 In general, methods for detecting a polynucleotide of the invention can comprise  
contacting a sample with a compound that binds to and forms a complex with the  
polynucleotide for a period sufficient to form the complex, and detecting the complex,  
so that if a complex is detected, a polynucleotide of the invention is detected in the  
sample. Such methods can also comprise contacting a sample under stringent  
hybridization conditions with nucleic acid primers that anneal to a polynucleotide of the  
20 invention under such conditions, and amplifying annealed polynucleotides, so that if a  
polynucleotide is amplified, a polynucleotide of the invention is detected in the sample.

In general, methods for detecting a polypeptide of the invention can comprise  
contacting a sample with a compound that binds to and forms a complex with the  
polypeptide for a period sufficient to form the complex, and detecting the complex, so  
25 that if a complex is detected, a polypeptide of the invention is detected in the sample.

In detail, such methods comprise incubating a test sample with one or more of  
the antibodies or one or more of the nucleic acid probes of the present invention and  
assaying for binding of the nucleic acid probes or antibodies to components within the  
test sample.

Conditions for incubating a nucleic acid probe or antibody with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid probe or antibody used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification or immunological assay formats can readily be adapted to employ the nucleic acid probes or antibodies of the present invention. Examples of such assays can be found in Chard, T., An Introduction to Radioimmunoassay and Related Techniques, Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G.R. et al., Techniques in Immunocytochemistry, Academic Press, Orlando, FL Vol. 1 (1982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., Practice and Theory of immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1985). The test samples of the present invention include cells, protein or membrane extracts of cells, or biological fluids such as sputum, blood, serum, plasma, or urine. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are well known in the art and can be readily be adapted in order to obtain a sample which is compatible with the system utilized.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention. Specifically, the invention provides a compartment kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the probes or antibodies of the present invention; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound probe or antibody.

In detail, a compartment kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are

not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the antibodies used in the assay, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound antibody or probe. Types of detection reagents include labeled nucleic acid probes, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. One skilled in the art will readily recognize that the disclosed probes and antibodies of the present invention can be readily incorporated into one of the established kit formats which are well known in the art.

#### 4.14 MEDICAL IMAGING

The novel polypeptides and binding partners of the invention are useful in medical imaging of sites expressing the molecules of the invention (e.g., where the polypeptide of the invention is involved in the immune response, for imaging sites of inflammation or infection). See, e.g., Kunkel et al., U.S. Pat. NO. 5,413,778. Such methods involve chemical attachment of a labeling or imaging agent, administration of the labeled polypeptide to a subject in a pharmaceutically acceptable carrier, and imaging the labeled polypeptide *in vivo* at the target site.

#### 4.15 SCREENING ASSAYS

Using the isolated proteins and polynucleotides of the invention, the present invention further provides methods of obtaining and identifying agents which bind to a polypeptide encoded by an ORF corresponding to any of the nucleotide sequences set forth in the SEQ ID NOs: 1 - 164, or bind to a specific domain of the polypeptide encoded by the nucleic acid. In detail, said method comprises the steps of:

- (a) contacting an agent with an isolated protein encoded by an ORF of the present invention, or nucleic acid of the invention; and
- (b) determining whether the agent binds to said protein or said nucleic acid.

5 In general, therefore, such methods for identifying compounds that bind to a polynucleotide of the invention can comprise contacting a compound with a polynucleotide of the invention for a time sufficient to form a polynucleotide/compound complex, and detecting the complex, so that if a polynucleotide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

10 Likewise, in general, therefore, such methods for identifying compounds that bind to a polypeptide of the invention can comprise contacting a compound with a polypeptide of the invention for a time sufficient to form a polypeptide/compound complex, and detecting the complex, so that if a polypeptide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

15 Methods for identifying compounds that bind to a polypeptide of the invention can also comprise contacting a compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a receptor gene sequence in the cell, and detecting the complex by detecting reporter gene sequence expression, so that if a polypeptide/compound complex is detected, a compound that binds a polypeptide of the invention is identified.

20 Compounds identified via such methods can include compounds which modulate the activity of a polypeptide of the invention (that is, increase or decrease its activity, relative to activity observed in the absence of the compound). Alternatively, compounds identified via such methods can include compounds which modulate the expression of a polynucleotide of the invention (that is, increase or decrease expression relative to expression levels observed in the absence of the compound). Compounds, such as compounds identified via the methods of the invention, can be tested using standard assays well known to those of skill in the art for their ability to modulate activity/expression.

The agents screened in the above assay can be, but are not limited to, peptides, carbohydrates, vitamin derivatives, or other pharmaceutical agents. The agents can be selected and screened at random or rationally selected or designed using protein modeling techniques.

For random screening, agents such as peptides, carbohydrates, pharmaceutical agents and the like are selected at random and are assayed for their ability to bind to the protein encoded by the ORF of the present invention. Alternatively, agents may be rationally selected or designed. As used herein, an agent is said to be "rationally selected or designed" when the agent is chosen based on the configuration of the particular protein. For example, one skilled in the art can readily adapt currently available procedures to generate peptides, pharmaceutical agents and the like, capable of binding to a specific peptide sequence, in order to generate rationally designed antipeptide peptides, for example see Hurby et al., Application of Synthetic Peptides: Antisense Peptides," In Synthetic Peptides, A User's Guide, W.H. Freeman, NY (1992), pp. 289-307, and Kaspczak et al., Biochemistry 28:9230-8 (1989), or pharmaceutical agents, or the like.

In addition to the foregoing, one class of agents of the present invention, as broadly described, can be used to control gene expression through binding to one of the ORFs or EMFs of the present invention. As described above, such agents can be randomly screened or rationally designed/selected. Targeting the ORF or EMF allows a skilled artisan to design sequence specific or element specific agents, modulating the expression of either a single ORF or multiple ORFs which rely on the same EMF for expression control. One class of DNA binding agents are agents which contain base residues which hybridize or form a triple helix formation by binding to DNA or RNA. Such agents can be based on the classic phosphodiester, ribonucleic acid backbone, or can be a variety of sulfhydryl or polymeric derivatives which have base attachment capacity.

Agents suitable for use in these methods preferably contain 20 to 40 bases and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while



antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide and other DNA binding agents.

Agents which bind to a protein encoded by one of the ORFs of the present invention can be used as a diagnostic agent. Agents which bind to a protein encoded by one of the ORFs of the present invention can be formulated using known techniques to generate a pharmaceutical composition.

#### 4.16 USE OF NUCLEIC ACIDS AS PROBES

Another aspect of the subject invention is to provide for polypeptide-specific nucleic acid hybridization probes capable of hybridizing with naturally occurring nucleotide sequences. The hybridization probes of the subject invention may be derived from any of the nucleotide sequences SEQ ID NOs: 1 - 164. Because the corresponding gene is only expressed in a limited number of tissues, a hybridization probe derived from any of the nucleotide sequences SEQ ID NOs: 1 - 164 can be used as an indicator of the presence of RNA of cell type of such a tissue in a sample.

Any suitable hybridization technique can be employed, such as, for example, in situ hybridization. PCR as described in US Patents Nos. 4,683,195 and 4,965,188 provides additional uses for oligonucleotides based upon the nucleotide sequences. Such probes used in PCR may be of recombinant origin, may be chemically synthesized, or a mixture of both. The probe will comprise a discrete nucleotide sequence for the detection of identical sequences or a degenerate pool of possible sequences for identification of closely related genomic sequences.

Other means for producing specific hybridization probes for nucleic acids include the cloning of nucleic acid sequences into vectors for the production of mRNA probes. Such vectors are known in the art and are commercially available and may be used to synthesize RNA probes *in vitro* by means of the addition of the appropriate RNA polymerase as T7 or SP6 RNA polymerase and the appropriate radioactively labeled nucleotides. The nucleotide sequences may be used to construct hybridization

probes for mapping their respective genomic sequences. The nucleotide sequence provided herein may be mapped to a chromosome or specific regions of a chromosome using well known genetic and/or chromosomal mapping techniques. These techniques include in situ hybridization, linkage analysis against known chromosomal markers, hybridization screening with libraries or flow-sorted chromosomal preparations specific to known chromosomes, and the like. The technique of fluorescent in situ hybridization of chromosome spreads has been described, among other places, in Verma et al (1988) Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York NY.

Fluorescent *in situ* hybridization of chromosomal preparations and other physical chromosome mapping techniques may be correlated with additional genetic map data. Examples of genetic map data can be found in the 1994 Genome Issue of Science (265:1981f). Correlation between the location of a nucleic acid on a physical chromosomal map and a specific disease (or predisposition to a specific disease) may help delimit the region of DNA associated with that genetic disease. The nucleotide sequences of the subject invention may be used to detect differences in gene sequences between normal, carrier or affected individuals.

#### 4.17 PREPARATION OF SUPPORT BOUND OLIGONUCLEOTIDES

Oligonucleotides, i.e., small nucleic acid segments, may be readily prepared by, for example, directly synthesizing the oligonucleotide by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer.

Support bound oligonucleotides may be prepared by any of the methods known to those of skill in the art using any suitable support such as glass, polystyrene or Teflon. One strategy is to precisely spot oligonucleotides synthesized by standard synthesizers. Immobilization can be achieved using passive adsorption (Inouye & Hondo, (1990) J. Clin. Microbiol. 28(6) 1469-72); using UV light (Nagata *et al.*, 1985; Dahlen *et al.*, 1987; Morrissey & Collins, (1989) Mol. Cell Probes 3(2) 189-207) or by covalent binding of base modified DNA (Keller *et al.*, 1988; 1989); all references being specifically incorporated herein.

Another strategy that may be employed is the use of the strong biotin-streptavidin interaction as a linker. For example, Broude *et al.* (1994) Proc. Natl. Acad. Sci. USA 91(8) 3072-6, describe the use of biotinylated probes, although these are duplex probes, that are immobilized on streptavidin-coated magnetic beads. Streptavidin-coated beads  
5 may be purchased from Dynal, Oslo. Of course, this same linking chemistry is applicable to coating any surface with streptavidin. Biotinylated probes may be purchased from various sources, such as, e.g., Operon Technologies (Alameda, CA).

Nunc Laboratories (Naperville, IL) is also selling suitable material that could be used. Nunc Laboratories have developed a method by which DNA can be covalently  
10 bound to the microwell surface termed CovaLink NH. CovaLink NH is a polystyrene surface grafted with secondary amino groups ( $>NH$ ) that serve as bridge-heads for further covalent coupling. CovaLink Modules may be purchased from Nunc Laboratories. DNA molecules may be bound to CovaLink exclusively at the 5'-end by a phosphoramidate bond, allowing immobilization of more than 1 pmol of DNA  
15 (Rasmussen *et al.*, (1991) Anal. Biochem. 198(1) 138-42).

The use of CovaLink NH strips for covalent binding of DNA molecules at the 5'-end has been described (Rasmussen *et al.*, (1991). In this technology, a phosphoramidate bond is employed (Chu *et al.*, (1983) Nucleic Acids Res. 11(8) 6513-29). This is beneficial as immobilization using only a single covalent bond is preferred.  
20 The phosphoramidate bond joins the DNA to the CovaLink NH secondary amino groups that are positioned at the end of spacer arms covalently grafted onto the polystyrene surface through a 2 nm long spacer arm. To link an oligonucleotide to CovaLink NH via an phosphoramidate bond, the oligonucleotide terminus must have a 5'-end phosphate group. It is, perhaps, even possible for biotin to be covalently bound to CovaLink and  
25 then streptavidin used to bind the probes.

More specifically, the linkage method includes dissolving DNA in water (7.5 ng/ul) and denaturing for 10 min. at 95°C and cooling on ice for 10 min. Ice-cold 0.1 M 1-methylimidazole, pH 7.0 (1-MeIm<sub>7</sub>), is then added to a final concentration of 10 mM 1-MeIm<sub>7</sub>. A ss DNA solution is then dispensed into CovaLink NH strips (75 ul/well)  
30 standing on ice.

Carbodiimide 0.2 M 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), dissolved in 10 mM 1-MeIm<sub>7</sub>, is made fresh and 25 ul added per well. The strips are incubated for 5 hours at 50°C. After incubation the strips are washed using, e.g., Nunc-Immuno Wash; first the wells are washed 3 times, then they are soaked with washing solution for 5 min., and finally they are washed 3 times (where in the washing solution is 0.4 N NaOH, 0.25% SDS heated to 50°C).

It is contemplated that a further suitable method for use with the present invention is that described in PCT Patent Application WO 90/03382 (Southern & Maskos), incorporated herein by reference. This method of preparing an oligonucleotide bound to a support involves attaching a nucleoside 3'-reagent through the phosphate group by a covalent phosphodiester link to aliphatic hydroxyl groups carried by the support. The oligonucleotide is then synthesized on the supported nucleoside and protecting groups removed from the synthetic oligonucleotide chain under standard conditions that do not cleave the oligonucleotide from the support. Suitable reagents include nucleoside phosphoramidite and nucleoside hydrogen phosphorate.

An on-chip strategy for the preparation of DNA probe for the preparation of DNA probe arrays may be employed. For example, addressable laser-activated photodeprotection may be employed in the chemical synthesis of oligonucleotides directly on a glass surface, as described by Fodor *et al.* (1991) Science 251(4995) 767-73, incorporated herein by reference. Probes may also be immobilized on nylon supports as described by Van Ness *et al.* (1991) Nucleic Acids Res. 19(12) 3345-50; or linked to Teflon using the method of Duncan & Cavalier (1988) Anal. Biochem. 169(1) 104-8; all references being specifically incorporated herein.

To link an oligonucleotide to a nylon support, as described by Van Ness *et al.* (1991), requires activation of the nylon surface via alkylation and selective activation of the 5'-amine of oligonucleotides with cyanuric chloride.

One particular way to prepare support bound oligonucleotides is to utilize the light-generated synthesis described by Pease *et al.*, (1994) PNAS USA 91(11) 5022-6, incorporated herein by reference). These authors used current photolithographic techniques to generate arrays of immobilized oligonucleotide probes (DNA chips). These

methods, in which light is used to direct the synthesis of oligonucleotide probes in high-density, miniaturized arrays, utilize photolabile 5'-protected *N*-acyl-deoxynucleoside phosphoramidites, surface linker chemistry and versatile combinatorial synthesis strategies. A matrix of 256 spatially defined oligonucleotide probes may be generated in this manner.

#### 4.18 PREPARATION OF NUCLEIC ACID FRAGMENTS

The nucleic acids may be obtained from any appropriate source, such as cDNAs, genomic DNA, chromosomal DNA, microdissected chromosome bands, cosmid or YAC inserts, and RNA, including mRNA without any amplification steps. For example, Sambrook *et al.* (1989) describes three protocols for the isolation of high molecular weight DNA from mammalian cells (p. 9.14-9.23).

DNA fragments may be prepared as clones in M13, plasmid or lambda vectors and/or prepared directly from genomic DNA or cDNA by PCR or other amplification methods. Samples may be prepared or dispensed in multiwell plates. About 100-1000 ng of DNA samples may be prepared in 2-500 ml of final volume.

The nucleic acids would then be fragmented by any of the methods known to those of skill in the art including, for example, using restriction enzymes as described at 9.24-9.28 of Sambrook *et al.* (1989), shearing by ultrasound and NaOH treatment.

Low pressure shearing is also appropriate, as described by Schriefer *et al.* (1990) Nucleic Acids Res. 18(24) 7455-6, incorporated herein by reference). In this method, DNA samples are passed through a small French pressure cell at a variety of low to intermediate pressures. A lever device allows controlled application of low to intermediate pressures to the cell. The results of these studies indicate that low-pressure shearing is a useful alternative to sonic and enzymatic DNA fragmentation methods.

One particularly suitable way for fragmenting DNA is contemplated to be that using the two base recognition endonuclease, *Cvi*II, described by Fitzgerald *et al.* (1992) Nucleic Acids Res. 20(14) 3753-62. These authors described an approach for the rapid fragmentation and fractionation of DNA into particular sizes that they contemplated to be suitable for shotgun cloning and sequencing.

The restriction endonuclease *Cvi*JI normally cleaves the recognition sequence PuGCPy between the G and C to leave blunt ends. Atypical reaction conditions, which alter the specificity of this enzyme (*Cvi*JI\*\*), yield a quasi-random distribution of DNA fragments from the small molecule pUC19 (2688 base pairs). Fitzgerald *et al.* (1992) quantitatively evaluated the randomness of this fragmentation strategy, using a *Cvi*JI\*\* digest of pUC19 that was size fractionated by a rapid gel filtration method and directly ligated, without end repair, to a lac Z minus M13 cloning vector. Sequence analysis of 76 clones showed that *Cvi*JI\*\* restricts pyGCPy and PuGCPu, in addition to PuGCPy sites, and that new sequence data is accumulated at a rate consistent with random fragmentation.

As reported in the literature, advantages of this approach compared to sonication and agarose gel fractionation include: smaller amounts of DNA are required (0.2-0.5 ug instead of 2-5 ug); and fewer steps are involved (no preligation, end repair, chemical extraction, or agarose gel electrophoresis and elution are needed).

Irrespective of the manner in which the nucleic acid fragments are obtained or prepared, it is important to denature the DNA to give single stranded pieces available for hybridization. This is achieved by incubating the DNA solution for 2-5 minutes at 80-90°C. The solution is then cooled quickly to 2°C to prevent renaturation of the DNA fragments before they are contacted with the chip. Phosphate groups must also be removed from genomic DNA by methods known in the art.

#### 4.19 PREPARATION OF DNA ARRAYS

Arrays may be prepared by spotting DNA samples on a support such as a nylon membrane. Spotting may be performed by using arrays of metal pins (the positions of which correspond to an array of wells in a microtiter plate) to repeated by transfer of about 20 nl of a DNA solution to a nylon membrane. By offset printing, a density of dots higher than the density of the wells is achieved. One to 25 dots may be accommodated in 1 mm<sup>2</sup>, depending on the type of label used. By avoiding spotting in some preselected number of rows and columns, separate subsets (subarrays) may be formed. Samples in one subarray may be the same genomic segment of DNA (or the same gene) from different individuals, or may be different, overlapped genomic clones. Each of the subarrays may

represent replica spotting of the same samples. In one example, a selected gene segment may be amplified from 64 patients. For each patient, the amplified gene segment may be in one 96-well plate (all 96 wells containing the same sample). A plate for each of the 64 patients is prepared. By using a 96-pin device, all samples may be spotted on one 8 x 12 cm membrane. Subarrays may contain 64 samples, one from each patient. Where the 96 subarrays are identical, the dot span may be 1 mm<sup>2</sup> and there may be a 1 mm space between subarrays.

Another approach is to use membranes or plates (available from NUNC, Naperville, Illinois) which may be partitioned by physical spacers e.g. a plastic grid molded over the membrane, the grid being similar to the sort of membrane applied to the bottom of multiwell plates, or hydrophobic strips. A fixed physical spacer is not preferred for imaging by exposure to flat phosphor-storage screens or x-ray films.

The present invention is illustrated in the following examples. Upon consideration of the present disclosure, one of skill in the art will appreciate that many other embodiments and variations may be made in the scope of the present invention. Accordingly, it is intended that the broader aspects of the present invention not be limited to the disclosure of the following examples. The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention, and compositions and methods which are functionally equivalent are within the scope of the invention. Indeed, numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the present preferred embodiments. Consequently, the only limitations which should be placed upon the scope of the invention are those which appear in the appended claims.

All references cited within the body of the instant specification are hereby incorporated by reference in their entirety.

## **5.0 EXAMPLES**

### **5.1 EXAMPLE 1**

#### **Novel Nucleic Acid Sequences Obtained From Various Libraries**

A plurality of novel nucleic acids were obtained from cDNA libraries prepared from various human tissues and in some cases isolated from a genomic library derived from human chromosome using standard PCR, SBH sequence signature analysis and Sanger sequencing techniques. The inserts of the library were amplified with PCR using  
5 primers specific for the vector sequences which flank the inserts. Clones from cDNA libraries were spotted on nylon membrane filters and screened with oligonucleotide probes (e.g., 7-mers) to obtain signature sequences. The clones were clustered into groups of similar or identical sequences. Representative clones were selected for sequencing.

In some cases, the 5' sequence of the amplified inserts was then deduced using a  
10 typical Sanger sequencing protocol. PCR products were purified and subjected to fluorescent dye terminator cycle sequencing. Single pass gel sequencing was done using a 377 Applied Biosystems (ABI) sequencer to obtain the novel nucleic acid sequences. In some cases RACE (Random Amplification of cDNA Ends) was performed to further extend the sequence in the 5' direction.

## 15 **5.2 EXAMPLE 2**

### **Novel Nucleic Acids**

The novel nucleic acids of the present invention of the invention were assembled from sequences that were obtained from a cDNA library by methods described in Example 1 above, and in some cases sequences obtained from one or more public  
20 databases. The nucleic acids were assembled using an EST sequence as a seed. Then a recursive algorithm was used to extend the seed EST into an extended assemblage, by pulling additional sequences from different databases (i.e., Hyseq's database containing EST sequences, dbEST version 114, gb pri 114, and UniGene version 101) that belong to this assemblage. The algorithm terminated when there was no additional sequences from  
25 the above databases that would extend the assemblage. Inclusion of component sequences into the assemblage was based on a BLASTN hit to the extending assemblage with BLAST score greater than 300 and percent identity greater than 95%.

Using PHRAP (Univ. of Washington) or CAP4 (Paracel), a full length gene cDNA sequence and its corresponding protein sequence were generated from the



5 assemblage. Any frame shifts and incorrect stop codons were corrected by hand editing. During editing, the sequence was checked using FASTY and/or BLAST against Genbank (i.e., dbEST version 118, gb pri 118, UniGene version 118, Genepet release 118). Other computer programs which may have been used in the editing process were phredPhrap and Consed (University of Washington) and ed-ready, ed-ext and gc-zip-2 (Hyseq, Inc.). The full-length nucleotide and amino acid sequences, including splice variants resulting from these procedures are shown in the Sequence Listing as SEQ ID NOS:1- 164.

Table 1 shows the various tissue sources of SEQ ID NO: 1-164.

10 The nearest neighbor results for SEQ ID NO: 1-164 were obtained by a BLASTP version 2.0a1 19MP-WashU search against Genpept release 118, using BLAST algorithm. The nearest neighbor result showed the closest homologue for SEQ ID NO: 1-164 from Genpept (and contains the translated amino acid sequences for which the nucleic acid sequence encodes). The nearest neighbor results for SEQ ID NO: 1-164 are shown in Table 2 below.

15

TABLE 1

TISSUE ORIGIN	RNA SOURCE	HYSEQ LIBRARY NAME	SEQ ID NOS:
adult brain	GIBCO	AB3001	4 13-14 19-20 36-37 50 56 73 76 82 93 95 105 127-128 131 134 137 159
adult brain	GIBCO	ABD003	1-4 14 18 23 27 33 36-39 47 51-52 56 58 63-65 71 73 79 82 90 93-94 98 105-106 109-110 115 121 130-131 135 137 141 144-145 159 164
adult brain	Clontech	ABR001	2 18-20 24 30 34 112 131 140- 141
adult brain	Clontech	ABR006	2-3 9 21 40 45 52 121 137 140 152 164
adult brain	Clontech	ABR008	1-3 6-7 9 14-15 23-25 27-29 33-34 36-40 43 46 52-53 55-56 60 63-64 66 68-69 75 77 79 90 92-93 95 98 100 104 106 110 114 117 119 121 127-132 136 140-150 152 155 159-160 164
adult brain	Clontech	ABR011	68
adult brain	Invitrogen	ABR013	21 24 60 114
adult brain	Invitrogen	ABR014	2-3 162
adult brain	Invitrogen	ABR016	1
adult brain	Invitrogen	ABT004	19-20 26-27 31-35 46 56 63-65 87-90 93 110-111 118 127-128 142-143 152 159
cultured preadipocytes	Stratagene	ADP001	3 68 76 82 121 141 157
adrenal gland	Clontech	ADR002	1 9 13 33 43 51-52 73 79 90 93 97 121 124-125 130
adult heart	GIBCO	AHR001	2-4 9 24 36-37 48-49 52-53 64 71 73-74 76 79 82 93 95-96 101 110-111 121 125-126 130 134-135 137 139-140 142-143 153-154 156 159 162
adult kidney	GIBCO	AKD001	4-12 14 18 23 25 27 31 38 47 51 57-58 68 71 73 76-77 79 82 93 95-96 98 101 104 110-111 121 123 126-128 130-131 134- 135 137 141 147-149 152 155 157 159 163-164
adult kidney	Invitrogen	AKT002	1-2 4 18 23 31 71 76 82-83 100-101 111 121 127-128 137 148-149 159 163-164
adult lung	GIBCO	ALG001	5 25 33 51 68 79 95-96 98 109-110 135 155 159 162
lymph node	Clontech	ALN001	1 3 23 59 73 76 83 121 130 147 155 159
young liver	GIBCO	ALV001	2 30-31 45 52 64 79-81 86 98- 99 101-103 130 133 144-145
adult liver	Invitrogen	ALV002	1 18 27 45 56 79 82 86 90 95- 96 98 126 133 142-143 159
adult ovary	Invitrogen	AOV001	1-8 13-14 17-18 23 27 29-31 35 47-52 57-58 62 64-66 68 71 73 75-76 79 82-85 90 93 96 98

TABLE 1

			100-101 104-105 108-112 115-117 121-123 125 127-128 130-131 135 137 140-145 147 153-156 159 162 164
adult placenta	Clontech	APL001	1 90 93 100 107
placenta	Invitrogen	APL002	3 27 51 56 93 131-132 157 162
adult spleen	GIBCO	ASP001	3-4 16 27 52 64 68 79 90 93 96 111 121 127-128 130 137 140-141 148-149 152 159 162 164
testis	GIBCO	ATS001	1-2 13 18 23 46-47 68 71 73 82 93 96 102-103 109-111 121 123 127-128 130 162
adult bladder	Invitrogen	BLD001	3 24 58 71 79 111 121
bone marrow	Clontech	BMD001	2-5 8 10-12 18 21 23 47 51-52 56 68 73-74 76 82 96 100 104 110 119-121 125 130-132 134 137 140 147 153 155-156 161-162
bone marrow	Clontech	BMD002	1 3-5 9-12 18 21 45 47 52 66 74 76 83 93 112 121 127-128 130-132 137 140 142-143 157 162
bone marrow	Clontech	BMD007	121 162
adult colon	Invitrogen	CLN001	65 95 121 148-150
Mixture of 16 tissues - mRNAs*	Various Vendors	CTL021	162
adult cervix	BioChain	CVX001	1-3 13-14 18 22 44-45 47-49 56 68 70-71 73 82 95 100-101 105 108 111 121 125-128 131-132 135 147 150 153 155-156 159
diaphragm	BioChain	DIA002	82
endothelial cells	Strategene	EDT001	1-4 6-7 13 18 23 26-28 30 36-37 45 51-52 55 58 61-62 64 68-69 71 76 79 82 93 95-96 98 100-101 104 110 119 121 125 127-128 131-132 134 137 140-141 147 150 155 159
fetal brain	Clontech	FBR001	79
fetal brain	Clontech	FBR004	14 21 82 104 121 140
fetal brain	Clontech	FBR006	1-4 6-9 14-15 33-35 42 52 56-57 69 77 79 90 93 98 101 110 114 119 121 124 127-128 130 147 152 160

\* The 16 tissue-mRNAs and their vendor source, are as follows: 1) Normal adult brain mRNA (Invitrogen), 2) normal adult kidney mRNA (Invitrogen), 3) normal adult liver mRNA (Invitrogen), 4) normal fetal brain mRNA (Invitrogen), 5) normal fetal kidney mRNA (Invitrogen), 6) normal fetal liver mRNA (Invitrogen), 7) normal fetal skin mRNA (Invitrogen), 8) human adrenal gland mRNA (Clontech), 9) human bone marrow mRNA (Clontech), 10) human leukemia lymphoblastic mRNA (Clontech), 11) human thymus mRNA (Clontech), 12) human lymph node mRNA (Clontech), 13) human spinal cord mRNA (Clontech), 14) human thyroid mRNA (Clontech), 15) human esophagus mRNA (BioChain), 16) human conceptional umbilical cord mRNA (BioChain).

TABLE 1

fetal brain	Invitrogen	FBT002	2-3 27 31 63-65 68 79 82 90 93 127-128 142-143 147 150
fetal heart	Invitrogen	FHR001	3 78
fetal kidney	Clontech	FKD001	52 77 121 130 137 150
fetal kidney	Clontech	FKD002	137
fetal kidney	Invitrogen	FKD007	121
fetal lung	Clontech	FLG001	3 5 68 148-149 159
fetal lung	Invitrogen	FLG003	3 82 93 98 111-112 130 136 138 148-149
fetal lung	Clontech	FLG004	3
fetal liver- spleen	Columbia University	FLS001	1-4 10-12 14 18 21 26-28 33 38 43 45 47 51-53 56-59 64-65 68 71 74 76 79-82 86 90 93 95-96 99 101-103 105 108-112 121-122 125 127-128 130-134 137 139-145 147 150 152 157 162 164
fetal liver- spleen	Columbia University	FLS002	1 3-4 10-13 16 18 25-26 28 39 42 51-52 56 58-59 64 68 71 76 79-83 86 90 93 98-99 101 108- 112 122 125-126 130-134 137 139-140 142-143 147 150 152 155 157 159
fetal liver- spleen	Columbia University	FLS003	4 16 162 164
fetal liver	Invitrogen	FLV001	3-4 16 25 28 31 58 64-65 79- 81 86 93 104 133 147-150 159 162
fetal liver	Clontech	FLV004	5 70 112
fetal muscle	Invitrogen	FMS001	6-7 22 36-37 44 82 90 93 98 102-103 121 127-128 139-140 144-145 157
fetal muscle	Invitrogen	FMS002	18 24 42 44-45 108 114 121 137
fetal skin	Invitrogen	FSK001	2-3 6-7 27 31 51 57 64 68 76 82 93 95 98 104 108 117 121- 122 127-128 135 138 142-143 147-150 157 159
fetal skin	Invitrogen	FSK002	1 5 44 74 127-128
fetal spleen	BioChain	FSP001	76
umbilical cord	BioChain	FUC001	2-3 8-9 27 31 41 52 56 71 82- 83 90 96 102-103 108 119 121 126-128 137 140-141 150-151 153-154 162
fetal brain	GIBCO	HFB001	1-4 8 13-15 18-20 23 33-34 36-37 47 52-53 57-58 65 68-69 71 73 79 82 93 98 100-101 105 108-109 115 121 125 127-128 130-131 134 140-141 144-145 152 155-156 159 161-162 164
macrophage	Invitrogen	HMP001	79 111
infant brain	Columbia University	IB2002	2-3 13-15 19-20 23 25 30 32 34-37 41 45-47 52-53 56-58 64-65 68-69 71 73 76-77 79 88 90 92 98 101-103 109-111 113 115 121 126-128 130 137 141-

TABLE 1

			145 147 150 153-154 159 164
infant brain	Columbia University	IB2003	3 19-20 27 34 41 45-47 52-53 56 58 65 68 72-74 77 90 98 126 130 141 153-154 159 164
infant brain	Columbia University	IBM002	3 121 126 140 155 160
infant brain	Columbia University	IBS001	19-20 35 41 56 61 144-145 159
lung, fibroblast	Strategene	LFB001	2 28 56 71 82 110 121
lung tumor	Invitrogen	LGT002	1-2 4 13 16 18-20 23 27-28 31 51-52 54 57-58 68 71 76 79 82 89 91 93 96 98 100 104 109- 111 121 126 130 134-135 141- 143 148-149 153-154 157-159
lymphocytes	ATCC	LPC001	2 30 41 52 56 68 73 82 93 109 119 121 130 137 140 148-149 162
leukocyte	GIBCO	LUC001	1-3 5 8-13 16 18 23 25-26 28- 29 31 41-42 45-49 51-52 56 58 62 64 66 68 73-74 76 79 82 90 93 96 98 101 105 109-111 121 125 127-128 130-132 137 140- 145 147-150 155 157 159 161- 162 164
leukocyte	Clontech	LUC003	1 3 9 23 43 101 121 157 162
melanoma from cell line ATCC #CRL 1424	Clontech	MEL004	1-2 4 19-20 23 69 82 111 121 130 150 153-154
mammary gland	Invitrogen	MMG001	1 3 6-7 19-20 27 30-31 46 55- 58 64-67 71 82 90 93 95 98 102-104 110-111 121 125 127- 128 132 137-138 141-145 147- 152 155 157 159-160 164
induced neuron cells	Strategene	NTD001	27 52 82 85 131
retinoid acid induced neuronal cells	Strategene	NTR001	33 68
neuronal cells	Strategene	NTU001	3 18 25 27 33 36-37 52 76 85 98 131 141
pituitary gland	Clontech	PIT004	19-20 27 127-128
placenta	Clontech	PLA003	130
prostate	Clontech	PRT001	4 10-12 18 23 53 56 65 73 96 100 121 138 141 155
rectum	Invitrogen	REC001	3 27 56 104 142-145 148-150
salivary gland	Clontech	SAL001	28 56 101 110 131 137
skin fibroblast	ATCC	SFB003	131 141
small intestine	Clontech	SIN001	3 8-9 28 58 98 138 140 144- 145 147
skeletal muscle	Clontech	SKM001	13 24 96 108 112 121
spinal cord	Clontech	SPC001	1 3 10-12 14 52 56 65 69-70 74 77 93 95 105 109 121-122

[illegible]

			131 140-141 147 153-154 162
adult spleen	Clontech	SPLc01	31 43 110
stomach	Clontech	STO001	2 36-37 73 125
thalamus	Clontech	THA002	24 28 58 65 69 130 141
thymus	Clontech	THM001	6-7 29 68 71 83 98 119 134 155
thymus	Clontech	THMc02	1 5 9 28 31 38 42 45 50 52-53 71 74 93 114 117 121-122 130- 131 137 142-145 147 150 158
thyroid gland	Clontech	THR001	2-3 13 23 30 36-37 47 52-53 56 65 71 77 79 82-83 96 98 102-103 105 108 110-111 121 127-128 130-131 141-143 146 153-155 157 159 162
trachea	Clontech	TRC001	8 16 50 54 73 82 96 102-103 148-149 162
uterus	Clontech	UTR001	3 27 71 83 98 121 137 140 162

TABLE 2

SEQ ID NO	CORRESPONDING SEQ ID NO. IN U.S.S.N. 09/560,875	ACCESSION NUMBER	DESCRIPTION	SMITH-WATERMAN SCORE	% IDENTITY
1	886	AE003680	Drosophila melanogaster CG8202 gene product	854	41
2	1028	Z11518	Homo sapiens histidyl-tRNA synthetase	2582	100
3	1916	X13916	Homo sapiens LDL-receptor related precursor (AA -19 to 4525)	25529	100
4	2072	AK000631	Homo sapiens unnamed protein product	2030	99
5	2424	U89345	Mus musculus cerebellar postnatal development protein-1	1246	91
6	2474	AL161578	Arabidopsis thaliana putative protein	335	46
7	2474	AL161578	Arabidopsis thaliana putative protein	333	47
8	2887	AB032948	Homo sapiens KIAA1122 protein	5280	99
9	3001	AF064782	Mus musculus unknown	1174	86
10	3182	AL080196	Homo sapiens hypothetical protein	4192	100
11	3182	AL080196	Homo sapiens hypothetical protein	3380	89
12	3182	AB040954	Homo sapiens KIAA1521 protein	3242	76
13	3193	AF196481	Homo sapiens RING finger protein; FXY2	3644	100
14	3196	AB007903	Homo sapiens KIAA0443	1610	54
15	3224	AB026187	Homo sapiens protocadherin-Xa	5244	100
16	3225	AB002405	Homo sapiens LAK-4p	498	42
17	3234	AB027289	Homo sapiens cyclin-E binding protein 1	5421	100
18	3241	AE003595	Drosophila melanogaster CG7414 gene product	978	39
19	3243	AJ245822	Homo sapiens type I transmembrane receptor	4560	100
20	3243	AJ245820	Homo sapiens type I transmembrane receptor	4624	100
21	3259	Z48042	Homo sapiens GPI-anchored protein p137	3340	99
22	3272	AL031782	Homo sapiens dJ708F5.1 (PUTATIVE novel Collagen alpha 1 LIKE protein)	2739	100
23	3278	AJ131245	Homo sapiens Sec24B	6602	100

TABLE 2

			protein		
24	3296	AK001027	Homo sapiens unnamed protein product	2108	99
25	3327	Y14690	Homo sapiens procollagen alpha 2 (V)	600	34
26	3334	AE003567	Drosophila melanogaster CG10673 gene product	497	45
27	3339	AE003620	Drosophila melanogaster CG8460 gene product	723	40
28	3347	Z49907	Caenorhabditis elegans B0491.1	804	42
29	3387	AB037852	Homo sapiens KIAA1431 protein	4754	100
30	3392	AL049482	Arabidopsis thaliana putative protein	436	47
31	3411	AC004528	Homo sapiens R32184_3	891	91
32	3427	AB037830	Homo sapiens KIAA1409 protein	7532	100
33	3432	X53793	Homo sapiens 5' half of the product is homologues to Bacillus subtilis SAICAR synthetase, 3' half corresponds to the catalytic subunit of AIR carboxylase	2232	100
34	3441	AB018316	Homo sapiens KIAA0773 protein	398	38
35	3479	Z75550	Caenorhabditis elegans weak similarity with BRKA gene from Bordetella Pertussis~cDNA EST EMBL:T01060 comes from this gene~cDNA EST EMBL:T01361 comes from this gene	933	44
36	3488	AB014567	Homo sapiens KIAA0667 protein	5598	99
37	3488	AB029324	Rattus norvegicus TIP120-family protein TIP120B	4961	90
38	3553	AF251040	Homo sapiens putative nuclear protein	2119	100
39	3560	AB014596	Homo sapiens KIAA0696 protein	2879	100
40	3618	U87305	Rattus norvegicus transmembrane receptor UNC5H1	3257	90
41	3642	AF118889	Rattus norvegicus b-tomomyosin isoform	3155	97
42	3649	AF226993	Rattus norvegicus	8793	95



TABLE 2

			selective LIM binding factor		
43	3676	U43585	Mus musculus protein kinase related to Raf protein kinases; Method: conceptual translation supplied by author	3312	88
44	3747	AL031782	Homo sapiens dJ708F5.1 (PUTATIVE novel Collagen alpha 1 LIKE protein)	1546	100
45	3917	AC002542	Homo sapiens similar to C. elegans F11A10.5; 80% similarity to Z68297 (PID:g1130619)	2294	100
46	4218	AL109827	Homo sapiens dJ309K20.3 (Copine I (similar to KIAA0636))	606	52
47	4219	X59131	Homo sapiens hypothetical protein	5705	99
48	4222	AL110188	Homo sapiens hypothetical protein	2994	100
49	4222	X52332	Homo sapiens zinc finger protein 10	2423	99
50	4229	Y09631	Homo sapiens PIBF1 protein	2935	99
51	4230	X71997	Rattus norvegicus myosin I	3883	98
52	4240	L08505	Rattus norvegicus dynein heavy chain	11097	98
53	4241	AF079529	Homo sapiens cAMP-specific phosphodiesterase 8B; PDE8B1; 3',5'-cyclic nucleotide phosphodiesterase	3487	100
54	4249	AF081947	Mus musculus tektin	1134	81
55	4252	AB037836	Homo sapiens KIAA1415 protein	871	100
56	4267	AB018313	Homo sapiens KIAA0770 protein	3830	100
57	4272	AF015770	Mus musculus radical fringe	1422	82
58	4273	X99270	Homo sapiens unknown	1545	99
59	4275	X77371	Mesocricetus auratus COR1	641	78
60	4283	AB014576	Homo sapiens KIAA0676 protein	296	79
61	4290	AK000956	Homo sapiens unnamed protein product	3318	99
62	4292	AF222980	Homo sapiens disrupted in Schizophrenia 1	4418	100

TABLE 2

			protein		
63	4305	Z31560	Homo sapiens sox-2	1683	100
64	4306	L07924	Mus musculus guanine nucleotide dissociation stimulator	3757	85
65	4308	AB041926	Homo sapiens GCK family kinase MINK-2	6866	100
66	4322	AE003815	Drosophila melanogaster CG8323 gene product	478	42
67	4351	AJ007012	Mus musculus Fish protein	704	94
68	4356	Z34289	Homo sapiens nucleolar phosphoprotein p130	3455	99
69	4399	U10991	Homo sapiens G2	8436	98
70	4400	AL080153	Homo sapiens hypothetical protein	2923	99
71	4520	X58288	Homo sapiens protein-tyrosine phosphatase	7734	99
72	4598	X56958	Homo sapiens ankyrin (brank-2)	9631	100
73	4599	AB029032	Homo sapiens KIAA1109 protein	10154	100
74	4600	D83197	Homo sapiens ankyrin repeat protein	802	99
75	4670	AF053711	Serinus canaria neurofilament medium subunit	192	31
76	4708	X78167	Rattus norvegicus ribosomal protein L15	990	96
77	4734	U76343	Homo sapiens GABA transport protein	2992	98
78	4738	Y13645	Homo sapiens uroplakin II	897	100
79	4749	D50913	Homo sapiens The KIAA0123 gene product is related to rat general mitochondrial matrix processing protease (MPP).	2710	99
80	4752	AF192522	Homo sapiens Niemann-Pick C3 protein; NPC3	7047	100
81	4752	AF192522	Homo sapiens Niemann-Pick C3 protein; NPC3	5472	100
82	4770	X60489	Homo sapiens elongation factor-1-beta	1162	100
83	4784	AC007204	Homo sapiens BC273239_1	2277	67
84	4785	AC003682	Homo sapiens R28830_1	2401	100
85	4792	AL117518	Homo sapiens hypothetical protein	353	61
86	4803	Z48475	Homo sapiens glucokinase regulator	3155	99

TABLE 2

87	4811	Z83844	Homo sapiens dJ37E16.2 (SH3-domain binding protein 1)	1884	98
88	4817	AF233323	Homo sapiens Fas-associated phosphatase-1	390	36
89	4818	AB037769	Homo sapiens KIAA1348 protein	574	100
90	4820	Y11411	Homo sapiens pristanoyl-CoA oxidase	3595	98
91	4831	M97188	Strongylocentrotus purpuratus tektin A1	290	46
92	4841	AB001105	Homo sapiens hippocalcin-like protein 4	995	100
93	4869	AJ243310	Homo sapiens C14orf3 protein	1795	100
94	4876	Z46972	Xenopus laevis homeobox protein	1279	91
95	4902	AF015264	Rattus norvegicus golgi peripheral membrane protein p65	1820	81
96	4910	X16901	Homo sapiens 30kb subunit of RAB30 /74	1284	100
97	4931	M12140	Homo sapiens envelope protein	202	81
98	5303	AL110193	Homo sapiens hypothetical protein	1964	99
99	5317	AL109983	Homo sapiens dJ718P11.1.1 (novel class II aminotransferase similar to serine palmitoyltransferase (isoform 1))	444	100
100	5322	M77183	Rattus norvegicus alpha-1-macroglobulin	227	45
101	5330	AB037806	Homo sapiens KIAA1385 protein	3785	100
102	5333	AL050095	Homo sapiens hypothetical protein	3265	100
103	5333	X82494	Homo sapiens fibulin-2	3407	99
104	5356	AF007872	Homo sapiens torsinB	160	40
105	5363	J03137	Bos taurus phospholipase C	6121	97
106	5364	AF073344	Homo sapiens ubiquitin-specific protease 3	256	43
107	5379	U05784	Rattus norvegicus light chain 3 subunit of microtubule-associated proteins 1A and 1B	257	51
108	5386	AK000282	Homo sapiens unnamed	1754	99

TABLE 2

			protein product		
109	5397	AB033115	Homo sapiens KIAA1289 protein	627	100
110	5401	AK001556	Homo sapiens unnamed protein product	3729	98
111	5419	AF182198	Homo sapiens intersectin 2 long isoform	8764	99
112	5420	L17308	Gossypium hirsutum proline-rich cell wall protein	192	35
113	5452	AF177169	Homo sapiens tropomodulin 2	1769	100
114	5467	AF083424	Ateline herpesvirus 3 orf 48	225	28
115	5482	AL049687	Homo sapiens hypothetical protein	2615	99
116	5483	AB037852	Homo sapiens KIAA1431 protein	327	80
117	5492	AK001154	Homo sapiens unnamed protein product	182	94
118	5499	D21211	Homo sapiens protein tyrosine phosphatase (PTP-BAS, type 3)	368	43
119	5525	U13045	Homo sapiens nuclear respiratory factor-2 subunit beta 1	869	62
120	5538	X52836	Homo sapiens tryptophan hydroxylase (AA 1 - 444)	2320	98
121	5539	X51466	Homo sapiens elongation factor 2	4460	100
122	5558	X82200	Homo sapiens gpStaf50	696	60
123	5559	X51760	Homo sapiens zinc finger protein (583 AA)	3130	100
124	5586	AB032984	Homo sapiens KIAA1158 protein	1024	100
125	5619	Z81036	Caenorhabditis elegans cDNA EST EMBL:M89190 comes from this gene-cDNA EST EMBL:T02289 comes from this gene-cDNA EST yk525h12.3 comes from this gene	177	32
126	5628	AB020598	Homo sapiens peptide transporter 3	3017	100
127	5640	AB033073	Homo sapiens KIAA1247 protein	3776	100
128	5640	AB033073	Homo sapiens KIAA1247 protein	2632	95
129	5827	AL033379	Homo sapiens dJ417022.2 (novel 7 transmembrane	2177	100

TABLE 2

			receptor (rhodopsin family) protein similar to high-affinity lysophosphatidic acid receptor homolog)		
130	6094	AJ000332	Homo sapiens Glucosidase II	5063	99
131	6195	AB041598	Mus musculus unnamed protein product	1249	67
132	6206	X57110	Homo sapiens c-cbl protein	4849	99
133	6355	X63652	Homo sapiens inter-alpha-trypsin inhibitor heavy chain ITIH1	3376	98
134	6362	X85134	Homo sapiens RB protein binding protein	2816	99
135	6386	L11672	Homo sapiens zinc finger protein	2047	58
136	6431	U91651	Plasmodium falciparum merozoite surface antigen 1	69	30
137	6457	X54871	Homo sapiens ras related protein Rab5b	1094	100
138	6480	Z98265	Homo sapiens plakophilin 3	4065	100
139	6497	AL035295	Homo sapiens hypothetical protein	959	99
140	6532	AB014566	Homo sapiens KIAA0666 protein	5462	99
141	6598	U18919	Homo sapiens unknown	1029	100
142	6644	D50925	Homo sapiens The KIAA0135 gene is related to pim-1 oncogene.	6495	99
143	6644	D50925	Homo sapiens The KIAA0135 gene is related to pim-1 oncogene.	6441	99
144	6645	AJ132545	Homo sapiens protein kinase	2921	100
145	6645	AJ132545	Homo sapiens protein kinase	1637	99
146	6761	AL121733	Homo sapiens hypothetical protein	1344	99
147	6782	AB002331	Homo sapiens KIAA0333	2571	100
148	6981	X87342	Homo sapiens Human giant larvae homologue	5317	99
149	6981	X87342	Homo sapiens Human giant larvae homologue	3495	96
150	7000	M94362	Homo sapiens lamin B2	2357	93
151	7029	AJ011654	Homo sapiens triple	3432	100

TABLE 2

			LIM domain protein		
152	7885	AB028945	Homo sapiens KIAA1022 protein	5800	99
153	8143	AF054986	Homo sapiens putative transmembrane GTPase	1816	100
154	8143	U95822	Homo sapiens putative transmembrane GTPase	1237	100
155	8234	Y11588	Homo sapiens apoptosis specific protein	1492	100
156	8463	X84195	Homo sapiens acylphosphatase	510	100
157	8467	U72882	Homo sapiens interferon-induced leucine zipper protein	1409	99
158	8540	AE000660	Homo sapiens hADV36S1	573	100
159	8600	AK000359	Homo sapiens unnamed protein product	2162	100
160	9656	AE001968	Deinococcus radiodurans hypothetical protein	147	27
161	9669	D13626	Homo sapiens KIAA0001	772	47
162	9695	U01317	Homo sapiens beta-globin	687	94
163	9744	X98333	Homo sapiens organic cation transporter	2933	100
164	9849	AE003749	Drosophila melanogaster CG13644 gene product	343	34

## CLAIMS

### WHAT IS CLAIMED IS:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1 – 164, a mature protein coding portion of  
5 SEQ ID NO: 1 - 164, an active domain of SEQ ID NO:1 - 164, and complementary sequences thereof.
2. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said polynucleotide hybridizes to the polynucleotide of claim 1 under  
10 stringent hybridization conditions.
3. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said polynucleotide has greater than about 90% sequence identity with the polynucleotide of claim 1.  
15
4. The polynucleotide of claim 1 wherein said polynucleotide is DNA.
5. An isolated polynucleotide of claim 1 wherein said polynucleotide comprises the complementary sequences.  
20
6. A vector comprising the polynucleotide of claim 1.
7. An expression vector comprising the polynucleotide of claim 1.
8. A host cell genetically engineered to comprise the polynucleotide of claim 1.  
25
9. A host cell genetically engineered to comprise the polynucleotide of claim 1 operatively associated with a regulatory sequence that modulates expression of the polynucleotide in the host cell.  
30
10. An isolated polypeptide, wherein the polypeptide is selected from the group consisting of:

- (a) a polypeptide encoded by any one of the polynucleotides of claim 1;  
and
- (b) a polypeptide encoded by a polynucleotide hybridizing under stringent conditions with any one of SEQ ID NO: 1 – 164.

5

11. A composition comprising the polypeptide of claim 10 and a carrier.

12. An antibody directed against the polypeptide of claim 10.

10 13. A method for detecting the polynucleotide of claim 1 in a sample, comprising:

a) contacting the sample with a compound that binds to and forms a complex with the polynucleotide of claim 1 for a period sufficient to form the complex; and

15 b) detecting the complex, so that if a complex is detected, the polynucleotide of claim 1 is detected.

14. A method for detecting the polynucleotide of claim 1 in a sample, comprising:

20 a) contacting the sample under stringent hybridization conditions with nucleic acid primers that anneal to the polynucleotide of claim 1 under such conditions;

b) amplifying a product comprising at least a portion of the polynucleotide of claim 1; and

25 c) detecting said product and thereby the polynucleotide of claim 1 in the sample.

30 15. The method of claim 14, wherein the polynucleotide is an RNA molecule and the method further comprises reverse transcribing an annealed RNA molecule into a cDNA polynucleotide.

16. A method for detecting the polypeptide of claim 10 in a sample, comprising:



a) contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex; and

5 b) detecting formation of the complex, so that if a complex formation is detected, the polypeptide of claim 10 is detected.

17. A method for identifying a compound that binds to the polypeptide of claim 10, comprising:

10 a) contacting the compound with the polypeptide of claim 10 under conditions sufficient to form a polypeptide/compound complex; and

b) detecting the complex, so that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.

15 18. A method for identifying a compound that binds to the polypeptide of claim 10, comprising:

a) contacting the compound with the polypeptide of claim 10, in a cell, under conditions sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and

20 b) detecting the complex by detecting reporter gene sequence expression, so that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.

19. A method of producing the polypeptide of claim 10, comprising,

25 a) culturing a host cell comprising a polynucleotide sequence selected from the group consisting of a polynucleotide sequence of SEQ ID NO: 1-164, a mature protein coding portion of SEQ ID NO: 1-164, an active domain of SEQ ID NO: 1-164, complementary sequences thereof and a polynucleotide sequence hybridizing under stringent conditions to SEQ ID NO: 1-164, under  
30 conditions sufficient to express the polypeptide in said cell; and

b) isolating the polypeptide from the cell culture or cells of step (a).

20. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of any one of the polypeptides from the Sequence Listing, the mature protein portion thereof, or the active domain thereof.

5

21. The polypeptide of claim 20 wherein the polypeptide is provided on a polypeptide array.

10

22. A collection of polynucleotides, wherein the collection comprising the sequence information of at least one of SEQ ID NO: 1 – 164.

23. The collection of claim 22, wherein the collection is provided on a nucleic acid array.

15

24. The collection of claim 23, wherein the array detects full-matches to any one of the polynucleotides in the collection.

25. The collection of claim 23, wherein the array detects mismatches to any one of the polynucleotides in the collection.

20

26. The collection of claim 22, wherein the collection is provided in a computer-readable format.

25

27. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.

30

28. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising an antibody that specifically binds to a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.

[illegible]

5

**DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY**

As [a] below named inventor(s), I/we hereby declare that:

**Y. Tom Tang, Chenghua Liu, Vinod Asundi, Ping Zhou, Jie Zhang, Feiyan Ren,  
Qing A. Zhao, Aidong J. Xue, Tom Wehrman, Jian-Rui Wang, Radoje T. Drmanac**

My/our residence, post office address and citizenship is/are as stated below next to my/our name(s).

I/we believe I/we am/are an/the original, first and sole/joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: NOVEL NUCLEIC ACIDS AND POLYPEPTIDES, the specification of which

  X   is attached hereto.

       was filed on [date] as Application Serial Number [            ]  
and was amended on [date].

I/We hereby state that I/we have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

I/We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I/We hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate, listed below and so identified, and I/we have also identified below any foreign application for patent or inventor's certificate on this invention filed by me or my legal representatives or assigns and having a filing date before that of the application on which priority is claimed:

NUMBER	COUNTRY	DAY/MONTH/ YEAR FILED	PRIORITY CLAIMED - YES OR NO

I/We hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I/we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

SERIAL NUMBER	FILING DATE	STATUS
09/560,875	April 27, 2000	Pending
09/496,914	February 03, 2000	Pending

I/We hereby declare that all statements made herein of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I/We hereby appoint the following attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith and request that all correspondence and telephone calls with respect to this application be directed to Leslie A. Mooi, HYSEQ, INC., 670 Almanor Avenue, Sunnyvale, CA 94085, Telephone No. (408) 524-8100:

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09/06/2010 09:43:50

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 Asundi, Vinod  
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 Zhang, Jie  
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 Zhao, Qing A.  
 Xue, Aidong J.  
 Wehrman, Tom  
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Phe	Ser	Ile	Val	Glu	Gln	Arg	Leu	Glu	Ala	Leu	Glu	Glu	Lys	Ile	Arg	
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Glu	Val	Asp	Val	Arg	Arg	Glu	Asp	Leu	Val	Glu	Glu	Ile	Lys	Arg	Arg	
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Thr	Gly	Gln	Pro	Leu	Cys	Ile	Cys	*								
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Pro Pro Leu Leu Leu Leu Leu Pro Leu Leu Ser Ala Leu Val Ala Ala	
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Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr Cys Ser Gln Leu	
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Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr Pro Thr Ser Thr	
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Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser Arg Cys Ile	
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Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser	
868 873 878 883	
gat gag gcc cca gcc ctc tgc cat cag cac acc tgc ccc tcg gac cga	3163
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1252 1257 1262 1267	
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Leu	His	Lys	Gly	Asp	Tyr	Ser	Val	Leu	Val	Pro	Gly	Leu	Arg	Asn	Thr	
1284					1289					1294					1299	
atc	gcc	ctg	gac	ttc	cac	ctc	agc	cag	agc	gcc	ctc	tac	tgg	acc	gac	4411
Ile	Ala	Leu	Asp	Phe	His	Leu	Ser	Gln	Ser	Ala	Leu	Tyr	Trp	Thr	Asp	
1300					1305					1310					1315	
gtg	gtg	gag	gac	aag	atc	tac	cgc	ggg	aag	ctg	ctg	gac	aac	gga	gcc	4459
Val	Val	Glu	Asp	Lys	Ile	Tyr	Arg	Gly	Lys	Leu	Leu	Asp	Asn	Gly	Ala	
1316					1321					1326					1331	
ctg	act	agt	ttc	gag	gtg	gtg	att	cag	tat	ggc	ctg	gcc	aca	ccc	gag	4507
Leu	Thr	Ser	Phe	Glu	Val	Val	Ile	Gln	Tyr	Gly	Leu	Ala	Thr	Pro	Glu	
1332					1337					1342					1347	
ggc	ctg	gct	gta	gac	tgg	att	gca	ggc	aac	atc	tac	tgg	gtg	gag	agt	4555
Gly	Leu	Ala	Val	Asp	Trp	Ile	Ala	Gly	Asn	Ile	Tyr	Trp	Val	Glu	Ser	
1348					1353					1358					1363	
aac	ctg	gat	cag	atc	gag	gtg	gcc	aag	ctg	gat	ggg	acc	ctc	cgg	acc	4603
Asn	Leu	Asp	Gln	Ile	Glu	Val	Ala	Lys	Leu	Asp	Gly	Thr	Leu	Arg	Thr	
1364					1369					1374					1379	
acc	ctg	ctg	gcc	ggt	gac	att	gag	cac	cca	agg	gca	atc	gca	ctg	gat	4651
Thr	Leu	Leu	Ala	Gly	Asp	Ile	Glu	His	Pro	Arg	Ala	Ile	Ala	Leu	Asp	
1380					1385					1390					1395	
ccc	cgg	gat	ggg	atc	ctg	ttt	tgg	aca	gac	tgg	gat	gcc	agc	ctg	ccc	4699
Pro	Arg	Asp	Gly	Ile	Leu	Phe	Trp	Thr	Asp	Trp	Asp	Ala	Ser	Leu	Pro	
1396					1401					1406					1411	
cgc	att	gag	gca	gcc	tcc	atg	agt	ggg	gct	ggg	cgc	cgc	acc	gtg	cac	4747
Arg	Ile	Glu	Ala	Ala	Ser	Met	Ser	Gly	Ala	Gly	Arg	Arg	Thr	Val	His	
1412					1417					1422					1427	
cgg	gag	acc	ggc	tct	ggg	ggc	tgg	ccc	aac	ggg	ctc	acc	gtg	gac	tac	4795
Arg	Glu	Thr	Gly	Ser	Gly	Gly	Trp	Pro	Asn	Gly	Leu	Thr	Val	Asp	Tyr	
1428					1433					1438					1443	
ctg	gag	aag	cgc	atc	ctt	tgg	att	gac	gcc	agg	tca	gat	gcc	att	tac	4843
Leu	Glu	Lys	Arg	Ile	Leu	Trp	Ile	Asp	Ala	Arg	Ser	Asp	Ala	Ile	Tyr	
1444					1449					1454					1459	
tca	gcc	cgt	tac	gac	ggc	tct	ggc	cac	atg	gag	gtg	ctt	cgg	gga	cac	4891
Ser	Ala	Arg	Tyr	Asp	Gly	Ser	Gly	His	Met	Glu	Val	Leu	Arg	Gly	His	
1460					1465					1470					1475	
gag	ttc	ctg	tcg	cac	ccg	ttt	gca	gtg	acg	ctg	tac	ggg	ggg	gag	gtc	4939
Glu	Phe	Leu	Ser	His	Pro	Phe	Ala	Val	Thr	Leu	Tyr	Gly	Gly	Glu	Val	
1476					1481					1486					1491	
tac	tgg	act	gac	tgg	cga	aca	aac	aca	ctg	gct	aag	gcc	aac	aag	tgg	4987
Tyr	Trp	Thr	Asp	Trp	Arg	Thr	Asn	Thr	Leu	Ala	Lys	Ala	Asn	Lys	Trp	



1492	1497	1502	1507	
acc ggc cac aat gtc acc gtg gta cag agg acc aac acc cag ccc ttt				5035
Thr Gly His Asn Val Thr Val Val Gln Arg Thr Asn Thr Gln Pro Phe				
1508	1513	1518	1523	
gac ctg cag gtg tac cac ccc tcc cgc cag ccc atg gct ccc aat ccc				5083
Asp Leu Gln Val Tyr His Pro Ser Arg Gln Pro Met Ala Pro Asn Pro				
1524	1529	1534	1539	
tgt gag gcc aat ggg ggc cag ggc ccc tgc tcc cac ctg tgt ctc atc				5131
Cys Glu Ala Asn Gly Gly Gln Gly Pro Cys Ser His Leu Cys Leu Ile				
1540	1545	1550	1555	
aac tac aac cgg acc gtg tcc tgc gcc tgc ccc cac ctc atg aag ctc				5179
Asn Tyr Asn Arg Thr Val Ser Cys Ala Cys Pro His Leu Met Lys Leu				
1556	1561	1566	1571	
cac aag gac aac acc acc tgc tat gag ttt aag aag ttc ctg ctg tac				5227
His Lys Asp Asn Thr Thr Cys Tyr Glu Phe Lys Lys Phe Leu Leu Tyr				
1572	1577	1582	1587	
gca cgt cag atg gag atc cga ggt gtg gac ctg gat gct ccc tac tac				5275
Ala Arg Gln Met Glu Ile Arg Gly Val Asp Leu Asp Ala Pro Tyr Tyr				
1588	1593	1598	1603	
aac tac atc atc tcc ttc acg gtg ccc gac atc gac aac gtc aca gtg				5323
Asn Tyr Ile Ile Ser Phe Thr Val Pro Asp Ile Asp Asn Val Thr Val				
1604	1609	1614	1619	
cta gac tac gat gcc cgc gag cag cgt gtg tac tgg tct gac gtg cgg				5371
Leu Asp Tyr Asp Ala Arg Glu Gln Arg Val Tyr Trp Ser Asp Val Arg				
1620	1625	1630	1635	
aca cag gcc atc aag cgg gcc ttc atc aac ggc aca ggc gtg gag aca				5419
Thr Gln Ala Ile Lys Arg Ala Phe Ile Asn Gly Thr Gly Val Glu Thr				
1636	1641	1646	1651	
gtc gtc tct gca gac ttg cca aat gcc cac ggg ctg gct gtg gac tgg				5467
Val Val Ser Ala Asp Leu Pro Asn Ala His Gly Leu Ala Val Asp Trp				
1652	1657	1662	1667	
gtc tcc cga aac ctg ttc tgg aca agc tat gac acc aat aag aag cag				5515
Val Ser Arg Asn Leu Phe Trp Thr Ser Tyr Asp Thr Asn Lys Lys Gln				
1668	1673	1678	1683	
atc aat gtg gcc cgg ctg gat ggc tcc ttc aag aac gca gtg gtg cag				5563
Ile Asn Val Ala Arg Leu Asp Gly Ser Phe Lys Asn Ala Val Val Gln				
1684	1689	1694	1699	
ggc ctg gag cag ccc cat ggc ctt gtc gtc cac cct ctg cgt ggg aag				5611
Gly Leu Glu Gln Pro His Gly Leu Val Val His Pro Leu Arg Gly Lys				
1700	1705	1710	1715	
ctc tac tgg acc gat ggt gac aac atc agc atg gcc aac atg gat ggc				5659
Leu Tyr Trp Thr Asp Gly Asp Asn Ile Ser Met Ala Asn Met Asp Gly				
1716	1721	1726	1731	

agc aat cgc acc ctg ctc ttc agt ggc cag aag ggc ccc gtg ggc ctg	5707
Ser Asn Arg Thr Leu Leu Phe Ser Gly Gln Lys Gly Pro Val Gly Leu	
1732 1737 1742 1747	
gct att gac ttc cct gaa agc aaa ctc tac tgg atc agc tcc ggg aac	5755
Ala Ile Asp Phe Pro Glu Ser Lys Leu Tyr Trp Ile Ser Ser Gly Asn	
1748 1753 1758 1763	
cat acc atc aac cgc tgc aac ctg gat ggg agt ggg ctg gag gtc atc	5803
His Thr Ile Asn Arg Cys Asn Leu Asp Gly Ser Gly Leu Glu Val Ile	
1764 1769 1774 1779	
gat gcc atg cgg agc cag ctg ggc aag gcc acc gcc ctg gcc atc atg	5851
Asp Ala Met Arg Ser Gln Leu Gly Lys Ala Thr Ala Leu Ala Ile Met	
1780 1785 1790 1795	
ggg gac aag ctg tgg tgg gct gat cag gtg tcg gaa aag atg ggc aca	5899
Gly Asp Lys Leu Trp Trp Ala Asp Gln Val Ser Glu Lys Met Gly Thr	
1796 1801 1806 1811	
tgc agc aag gct gac ggc tcg ggc tcc gtg gtc ctt cgg aac agc acc	5947
Cys Ser Lys Ala Asp Gly Ser Gly Ser Val Val Leu Arg Asn Ser Thr	
1812 1817 1822 1827	
acc ctg gtg atg cac atg aag gtc tat gac gag agc atc cag ctg gac	5995
Thr Leu Val Met His Met Lys Val Tyr Asp Glu Ser Ile Gln Leu Asp	
1828 1833 1838 1843	
cat aag ggc acc aac ccc tgc agt gtc aac aac ggt gac tgc tcc cag	6043
His Lys Gly Thr Asn Pro Cys Ser Val Asn Asn Gly Asp Cys Ser Gln	
1844 1849 1854 1859	
ctc tgc ctg ccc acg tca gag acg acc cgc tcc tgc atg tgc aca gcc	6091
Leu Cys Leu Pro Thr Ser Glu Thr Thr Arg Ser Cys Met Cys Thr Ala	
1860 1865 1870 1875	
ggc tat agc ctc cgg agt ggc cag cag gcc tgc gag ggc gta ggt tcc	6139
Gly Tyr Ser Leu Arg Ser Gly Gln Gln Ala Cys Glu Gly Val Gly Ser	
1876 1881 1886 1891	
ttt ctc ctg tac tct gtg cat gag gga atc agg gga att ccc ctg gat	6187
Phe Leu Leu Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro Leu Asp	
1892 1897 1902 1907	
ccc aat gac aag tca gat gcc ctg gtc cca gtg tcc ggg acc tcg ctg	6235
Pro Asn Asp Lys Ser Asp Ala Leu Val Pro Val Ser Gly Thr Ser Leu	
1908 1913 1918 1923	
gct gtc ggc atc gac ttc cac gct gaa aat gac acc atc tac tgg gtg	6283
Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr Ile Tyr Trp Val	
1924 1929 1934 1939	
gac atg ggc ctg agc acg atc agc cgg gcc aag cgg gac cag acg tgg	6331
Asp Met Gly Leu Ser Thr Ile Ser Arg Ala Lys Arg Asp Gln Thr Trp	
1940 1945 1950 1955	

cgt Arg 1956	gaa Glu	gac Asp	gtg Val	gtg Val	acc Thr 1961	aat Asn	ggc Gly	att Ile	ggc Gly	cgt Arg 1966	gtg Val	gag Glu	ggc Gly	att Ile	gca Ala 1971	6379
gtg Val 1972	gac Asp	tgg Trp	atc Ile	gca Ala	ggc Gly 1977	aac Asn	atc Ile	tac Tyr	tgg Trp	aca Thr 1982	gac Asp	cag Gln	ggc Gly	ttt Phe	gat Asp 1987	6427
gtc Val 1988	atc Ile	gag Glu	gtc Val	gcc Ala	cgg Arg 1993	ctc Leu	aat Asn	ggc Gly	tcc Ser	ttc Phe 1998	cgc Arg	tac Tyr	gtg Val	gtg Val	atc Ile 2003	6475
tcc Ser 2004	cag Gln	ggc Gly	cta Leu	gac Asp	aag Lys 2009	ccc Pro	cgg Arg	gcc Ala	atc Ile	acc Thr 2014	gtc Val	cac His	ccg Pro	gag Glu	aaa Lys 2019	6523
ggg Gly 2020	tac Tyr	ttg Leu	ttc Phe	tgg Trp	act Thr 2025	gag Glu	tgg Trp	ggc Gly	cag Gln	tat Tyr 2030	ccg Pro	cgt Arg	att Ile	gag Glu	cgg Arg 2035	6571
tct Ser 2036	cgg Arg	cta Leu	gat Asp	ggc Gly	acg Thr 2041	gag Glu	cgt Arg	gtg Val	gtg Val	ctg Leu 2046	gtc Val	aac Asn	gtc Val	agc Ser	atc Ile 2051	6619
agc Ser 2052	tgg Trp	ccc Pro	aac Asn	ggc Gly	atc Ile 2057	tca Ser	gtg Val	gac Asp	tac Tyr	cag Gln 2062	gat Asp	ggg Gly	aag Lys	ctg Leu	tac Tyr 2067	6667
tgg Trp 2068	tgc Cys	gat Asp	gca Ala	cgg Arg	aca Thr 2073	gac Asp	aag Lys	att Ile	gaa Glu	cgg Arg 2078	atc Ile	gac Asp	ctg Leu	gag Glu	aca Thr 2083	6715
ggc Gly 2084	gag Glu	aac Asn	cgc Arg	gag Glu	gtg Val 2089	gtt Val	ctg Leu	tcc Ser	agc Ser	aac Asn 2094	aac Asn	atg Met	gac Asp	atg Met	ttt Phe 2099	6763
tca Ser 2100	gtg Val	tct Ser	gtg Val	ttt Phe	gag Glu 2105	gat Asp	ttc Phe	atc Ile	tac Tyr	tgg Trp 2110	agt Ser	gac Asp	agg Arg	act Thr	cat His 2115	6811
gcc Ala 2116	aac Asn	ggc Gly	tct Ser	atc Ile	aag Lys 2121	cgc Arg	ggg Gly	agc Ser	aaa Lys	gac Asp 2126	aat Asn	gcc Ala	aca Thr	gac Asp	tcc Ser 2131	6859
gtg Val 2132	ccc Pro	ctg Leu	cga Arg	acc Thr	ggc Gly 2137	atc Ile	ggc Gly	gtc Val	cag Gln	ctt Leu 2142	aaa Lys	gac Asp	atc Ile	aaa Lys	gtc Val 2147	6907
ttc Phe 2148	aac Asn	cgg Arg	gac Asp	cgg Arg	cag Gln 2153	aaa Lys	ggc Gly	acc Thr	aac Asn	gtg Val 2158	tgc Cys	gcg Ala	gtg Val	gcc Ala	aat Asn 2163	6955
ggc Gly 2164	ggg Gly	tgc Cys	cag Gln	cag Gln	ctg Leu 2169	tgc Cys	ctg Leu	tac Tyr	cgg Arg	ggc Gly 2174	cgt Arg	ggg Gly	cag Gln	cgg Arg	gcc Ala 2179	7003
tgc Gly 2180	gcc Ala	tgt Cys	gcc Ala	cac Gln	ggg Leu	atg Cys	ctg Leu	gct Tyr	gaa Gln	gac Asp 2185	gga Gln	gca Ala	tcg Gln	tgc Cys	cgc Ala 2190	7051

Cys	Ala	Cys	Ala	His	Gly	Met	Leu	Ala	Glu	Asp	Gly	Ala	Ser	Cys	Arg	
2180					2185					2190					2195	
gag tat gcc ggc tac ctg ctc tac tca gag cgc acc att ctc aag agt 7099																
Glu Tyr Ala Gly Tyr Leu Leu Tyr Ser Glu Arg Thr Ile Leu Lys Ser																
2196					2201					2206					2211	
atc cac ctg tcg gat gag cgc aac ctc aat gcg ccc gtg cag ccc ttc 7147																
Ile His Leu Ser Asp Glu Arg Asn Leu Asn Ala Pro Val Gln Pro Phe																
2212					2217					2222					2227	
gag gac cct gag cac atg aag aac gtc atc gcc ctg gcc ttt gac tac 7195																
Glu Asp Pro Glu His Met Lys Asn Val Ile Ala Leu Ala Phe Asp Tyr																
2228					2233					2238					2243	
cgg gca ggc acc tct ccg ggc acc ccc aat cgc atc ttc ttc agc gac 7243																
Arg Ala Gly Thr Ser Pro Gly Thr Pro Asn Arg Ile Phe Phe Ser Asp																
2244					2249					2254					2259	
atc cac ttt ggg aac atc caa cag atc aac gac gat ggc tcc agg agg 7291																
Ile His Phe Gly Asn Ile Gln Gln Ile Asn Asp Asp Gly Ser Arg Arg																
2260					2265					2270					2275	
atc acc att gtg gaa aac gtg ggc tcc gtg gaa ggc ctg gcc tat cac 7339																
Ile Thr Ile Val Glu Asn Val Gly Ser Val Glu Gly Leu Ala Tyr His																
2276					2281					2286					2291	
cgt ggc tgg gac act ctc tat tgg aca agc tac acg aca tcc acc atc 7387																
Arg Gly Trp Asp Thr Leu Tyr Trp Thr Ser Tyr Thr Thr Ser Thr Ile																
2292					2297					2302					2307	
acg cgc cac aca gtg gac cag acc cgc cca ggg gcc ttc gag cgt gag 7435																
Thr Arg His Thr Val Asp Gln Thr Arg Pro Gly Ala Phe Glu Arg Glu																
2308					2313					2318					2323	
acc gtc atc act atg tct gga gat gac cac cca cgg gcc ttc gtt ttg 7483																
Thr Val Ile Thr Met Ser Gly Asp Asp His Pro Arg Ala Phe Val Leu																
2324					2329					2334					2339	
gac gag tgc cag aac ctc atg ttc tgg acc aac tgg aat gag cag cat 7531																
Asp Glu Cys Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Gln His																
2340					2345					2350					2355	
ccc agc atc atg cgg gcg gcg ctc tcg gga gcc aat gtc ctg acc ctt 7579																
Pro Ser Ile Met Arg Ala Ala Leu Ser Gly Ala Asn Val Leu Thr Leu																
2356					2361					2366					2371	
atc gag aag gac atc cgt acc ccc aat ggc ctg gcc atc gac cac cgt 7627																
Ile Glu Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala Ile Asp His Arg																
2372					2377					2382					2387	
gcc gag aag ctc tac ttc tct gac gcc acc ctg gac aag atc gag cgg 7675																
Ala Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp Lys Ile Glu Arg																
2388					2393					2398					2403	
tgc gag tat gac ggc tcc cac cgc tat gtg atc cta aag tca gag cct 7723																
Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu Lys Ser Glu Pro																

2404		2409		2414		2419	
gtc cac ccc ttc ggg ctg gcc gtg tat ggg gag cac att ttc tgg act							7771
Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His Ile Phe Trp Thr							
2420		2425		2430		2435	
gac tgg gtg cgg cgg gca gtg cag cgg gcc aac aag cac gtg ggc agc							7819
Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys His Val Gly Ser							
2436		2441		2446		2451	
aac atg aag ctg ctg cgc gtg gac atc ccc cag cag ccc atg ggc atc							7867
Asn Met Lys Leu Leu Arg Val Asp Ile Pro Gln Gln Pro Met Gly Ile							
2452		2457		2462		2467	
atc gcc gtg gcc aac gac acc aac agc tgt gaa ctc tct cca tgc cga							7915
Ile Ala Val Ala Asn Asp Thr Asn Ser Cys Glu Leu Ser Pro Cys Arg							
2468		2473		2478		2483	
atc aac aac ggt ggc tgc cag gac ctg tgt ctg ctc act cac cag ggc							7963
Ile Asn Asn Gly Gly Cys Gln Asp Leu Cys Leu Leu Thr His Gln Gly							
2484		2489		2494		2499	
cat gtc aac tgc tca tgc cga ggg ggc cga atc ctc cag gat gac ctc							8011
His Val Asn Cys Ser Cys Arg Gly Gly Arg Ile Leu Gln Asp Asp Leu							
2500		2505		2510		2515	
acc tgc cga gcg gtg aat tcc tct tgc cga gca caa gat gag ttt gag							8059
Thr Cys Arg Ala Val Asn Ser Ser Cys Arg Ala Gln Asp Glu Phe Glu							
2516		2521		2526		2531	
tgt gcc aat ggc gag tgc atc aac ttc agc ctg acc tgc gac ggc gtc							8107
Cys Ala Asn Gly Glu Cys Ile Asn Phe Ser Leu Thr Cys Asp Gly Val							
2532		2537		2542		2547	
ccc cac tgc aag gac aag tcc gat gag aag cca tcc tac tgc aac tcc							8155
Pro His Cys Lys Asp Lys Ser Asp Glu Lys Pro Ser Tyr Cys Asn Ser							
2548		2553		2558		2563	
cgc cgc tgc aag aag act ttc cgg cag tgc agc aat ggg cgc tgt gtg							8203
Arg Arg Cys Lys Lys Thr Phe Arg Gln Cys Ser Asn Gly Arg Cys Val							
2564		2569		2574		2579	
tcc aac atg ctg tgg tgc aac ggg gcc gac gac tgt ggg gat ggc tct							8251
Ser Asn Met Leu Trp Cys Asn Gly Ala Asp Asp Cys Gly Asp Gly Ser							
2580		2585		2590		2595	
gac gag atc cct tgc aac aag aca gcc tgt ggt gtg ggc gag ttc cgc							8299
Asp Glu Ile Pro Cys Asn Lys Thr Ala Cys Gly Val Gly Glu Phe Arg							
2596		2601		2606		2611	
tgc cgg gac ggg acc tgc atc ggg aac tcc agc cgc tgc aac cag ttt							8347
Cys Arg Asp Gly Thr Cys Ile Gly Asn Ser Ser Arg Cys Asn Gln Phe							
2612		2617		2622		2627	
gtg gat tgt gag gac gcc tca gat gag atg aac tgc agt gcc acc gac							8395
Val Asp Cys Glu Asp Ala Ser Asp Glu Met Asn Cys Ser Ala Thr Asp							
2628		2633		2638		2643	



ggg cgc tgt ctg agc tcc cgc cag tgg gag tgt gat ggc gag aat gac	9115
Gly Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp Gly Glu Asn Asp	
2868 2873 2878 2883	
tgc cac gac cag agt gac gag gct ccc aag aac cca cac tgc acc agc	9163
Cys His Asp Gln Ser Asp Glu Ala Pro Lys Asn Pro His Cys Thr Ser	
2884 2889 2894 2899	
cca gag cac aag tgc aat gcc tcg tca cag ttc ctg tgc agc agt ggg	9211
Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu Cys Ser Ser Gly	
2900 2905 2910 2915	
cgc tgt gtg gct gag gca ctg ctc tgc aac ggc cag gat gac tgt ggc	9259
Arg Cys Val Ala Glu Ala Leu Leu Cys Asn Gly Gln Asp Asp Cys Gly	
2916 2921 2926 2931	
gac agc tcg gac gag cgt ggc tgc cac atc aat gag tgt ctc agc cgc	9307
Asp Ser Ser Asp Glu Arg Gly Cys His Ile Asn Glu Cys Leu Ser Arg	
2932 2937 2942 2947	
aag ctc agt ggc tgc agc cag gac tgt gag gac ctc aag atc ggc ttc	9355
Lys Leu Ser Gly Cys Ser Gln Asp Cys Glu Asp Leu Lys Ile Gly Phe	
2948 2953 2958 2963	
aag tgc cgc tgt cgc cct ggc ttc cgg ctg aag gac gac ggc cgg acg	9403
Lys Cys Arg Cys Arg Pro Gly Phe Arg Leu Lys Asp Asp Gly Arg Thr	
2964 2969 2974 2979	
tgt gct gat gtg gac gag tgc agc acc acc ttc ccc tgc agc cag cgc	9451
Cys Ala Asp Val Asp Glu Cys Ser Thr Thr Phe Pro Cys Ser Gln Arg	
2980 2985 2990 2995	
tgc atc aac acc cat ggc agc tat aag tgt ctg tgt gtg gag ggc tat	9499
Cys Ile Asn Thr His Gly Ser Tyr Lys Cys Leu Cys Val Glu Gly Tyr	
2996 3001 3006 3011	
gca ccc cgc ggc ggc gac ccc cac agc tgc aag gct gtg act gac gag	9547
Ala Pro Arg Gly Gly Asp Pro His Ser Cys Lys Ala Val Thr Asp Glu	
3012 3017 3022 3027	
gaa ccg ttt ctg atc ttc gcc aac cgg tac tac ctg cgc aag ctc aac	9595
Glu Pro Phe Leu Ile Phe Ala Asn Arg Tyr Tyr Leu Arg Lys Leu Asn	
3028 3033 3038 3043	
ctg gac ggg tcc aac tac acg tta ctt aag cag ggc ctg aac aac gcc	9643
Leu Asp Gly Ser Asn Tyr Thr Leu Leu Lys Gln Gly Leu Asn Asn Ala	
3044 3049 3054 3059	
gtt gcc ttg gat ttt gac tac cga gag cag atg atc tac tgg aca gat	9691
Val Ala Leu Asp Phe Asp Tyr Arg Glu Gln Met Ile Tyr Trp Thr Asp	
3060 3065 3070 3075	
gtg acc acc cag ggc agc atg atc cga agg atg cac ctt aac ggg agc	9739
Val Thr Thr Gln Gly Ser Met Ile Arg Arg Met His Leu Asn Gly Ser	
3076 3081 3086 3091	
aat gtg cag gtc cta cac cgt aca ggc ctc agc aac ccc gat ggg ctg	9787

Asn Val Gln Val Leu His Arg Thr Gly Leu Ser Asn Pro Asp Gly Leu	
3092 3097 3102 3107	
gct gtg gac tgg gtg ggt ggc aac ctg tac tgg tgc gac aaa ggc cgg	9835
Ala Val Asp Trp Val Gly Gly Asn Leu Tyr Trp Cys Asp Lys Gly Arg	
3108 3113 3118 3123	
gac acc atc gag gtg tcc aag ctc aat ggg gcc tat cgg acg gtg ctg	9883
Asp Thr Ile Glu Val Ser Lys Leu Asn Gly Ala Tyr Arg Thr Val Leu	
3124 3129 3134 3139	
gtc agc tct ggc ctc cgt gag ccc agg gct ctg gtg gtg gat gtg cag	9931
Val Ser Ser Gly Leu Arg Glu Pro Arg Ala Leu Val Val Asp Val Gln	
3140 3145 3150 3155	
aat ggg tac ctg tac tgg aca gac tgg ggt gac cat tca ctg atc ggc	9979
Asn Gly Tyr Leu Tyr Trp Thr Asp Trp Gly Asp His Ser Leu Ile Gly	
3156 3161 3166 3171	
cgc atc ggc atg gat ggg tcc agc cgc agc gtc atc gtg gac acc aag	10027
Arg Ile Gly Met Asp Gly Ser Ser Arg Ser Val Ile Val Asp Thr Lys	
3172 3177 3182 3187	
atc aca tgg ccc aat ggc ctg acg ctg gac tat gtc act gag cgc atc	10075
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Lys Ser Ile Asn Arg Ala His Lys Thr Thr Gly Thr Asn Lys Thr Leu	
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Coulam et al. (2002)	
Study	1
Year	2002
Site	US
Study type	Retrospective
Study period	1996-2000
Study population	10,000
Study design	Case-control
Study objectives	To determine the risk of adverse drug reactions (ADRs) associated with the use of antipsychotic drugs in the elderly.
Study results	The study found that the use of antipsychotic drugs in the elderly was associated with a higher risk of ADRs compared to the use of these drugs in younger adults. The risk was highest for the use of high-potency antipsychotics.
Study conclusions	The study concluded that the use of antipsychotic drugs in the elderly should be carefully monitored for ADRs.
Study limitations	The study was limited by its retrospective design and the potential for confounding factors.
Study strengths	The study was a large, population-based study that included a wide range of antipsychotic drugs.
Study references	Coulam, C. C., et al. (2002). Adverse drug reactions in the elderly: A population-based study. <i>Journal of Clinical Pharmacy and Therapeutics</i> , 27(1), 1-8.

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Glu Ala Trp Gln Arg Asp Pro Ala Phe Ser Gly Leu Gln Arg Val Gly
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Gly Val Leu Thr Asp Leu Pro Cys Val Gly Val Ala Lys Lys Leu Leu
 98                               103                108                113

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Gln Val Asp Gly Leu Glu Asn Asn Ala Leu His Lys Glu Lys Ile Arg
114                               119                124                129

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Leu Leu Gln Thr Arg Gly Asp Ser Phe Pro Leu Leu Gly Asp Ser Gly
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act gtc ctg gga atg gcc ctg agg agc cac gac cgc agc acc agg ccc      535
Thr Val Leu Gly Met Ala Leu Arg Ser His Asp Arg Ser Thr Arg Pro
146                               151                156                161

ctc tac atc tcc gtg ggc cac agg atg agc ctg gag gcc gct gtg cgc      583
Leu Tyr Ile Ser Val Gly His Arg Met Ser Leu Glu Ala Ala Val Arg

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Asp Ser Gly Glu Ser Ser Ala Leu Cys \*

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Lys Ile Glu Glu Ala Pro Glu Ala Thr Pro Gln Pro Ser Gln Pro Gly

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Pro Ser Ser Pro Ile Ser Leu Ser Ala Glu Glu Glu Asn Ala Glu Gly

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Glu Asp Ser Ser Val Pro Glu Thr Pro Asp Asn Glu Arg Lys Ala Ser

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Ile Ser Tyr Phe Lys Asn Gln Arg Gly Ile Gln Tyr Ile Asp Leu Ser

80 85 90 95



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Ile Arg Glu Phe Ile Gln Asp Phe Gln Lys Leu Thr Ala Ala Asp Asp				
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aaa act gct cag gta gaa gat ttt ctg cag ttt ctt tat ggt gca atg				2545
Lys Thr Ala Gln Val Glu Asp Phe Leu Gln Phe Leu Tyr Gly Ala Met				
829	834	839	844	
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Ala Gln Asp Val Ile Trp Gln Asn Ala Ser Glu Glu Gln Leu Gln Asp				
845	850	855	860	
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Ala Gln Leu Ala Ile Glu Arg Ser Val Met Asn Arg Ile Phe Lys Leu				
861	866	871	876	
gcc ttc tac cct aat caa gat ggg gac ata ctt cgc gac cag gtt ctt				2689
Ala Phe Tyr Pro Asn Gln Asp Gly Asp Ile Leu Arg Asp Gln Val Leu				
877	882	887	892	
cat gaa cat atc cag aga ttg tct aaa gta gtg act gca aat cac aga				2737
His Glu His Ile Gln Arg Leu Ser Lys Val Val Thr Ala Asn His Arg				
893	898	903	908	
gct ctt cag ata cca gag gtt tat ctt cga gaa gca cca tgg cca tct				2785
Ala Leu Gln Ile Pro Glu Val Tyr Leu Arg Glu Ala Pro Trp Pro Ser				
909	914	919	924	
gca caa tca gaa atc agg aca ata agt gct tat aaa acc ccc cgg gac				2833
Ala Gln Ser Glu Ile Arg Thr Ile Ser Ala Tyr Lys Thr Pro Arg Asp				
925	930	935	940	

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Lys Val Gln Cys Ile Leu Arg Met Cys Ser Thr Ile Met Asn Leu Leu	
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Ser Leu Ala Asn Glu Asp Ser Val Pro Gly Ala Asp Asp Phe Val Pro	
957 962 967 972	
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Val Leu Val Phe Val Leu Ile Lys Ala Asn Pro Pro Cys Leu Leu Ser	
973 978 983 988	
act gtg cag tat atc agt agc ttt tat gct agc tgt ctg tct gga gag	3025
Thr Val Gln Tyr Ile Ser Ser Phe Tyr Ala Ser Cys Leu Ser Gly Glu	
989 994 999 1004	
gag tcc tat tgg tgg atg cag ttc aca gca gca gta gaa ttc att aaa	3073
Glu Ser Tyr Trp Trp Met Gln Phe Thr Ala Ala Val Glu Phe Ile Lys	
1005 1010 1015 1020	
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Thr Ile Asp Asp Arg Lys *	
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Phe Glu Asp Pro Leu Leu Leu Pro Cys Ala His Ser Leu Cys Phe Ser	
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Cys Ala His Arg Ile Leu Val Ser Ser Cys Ser Ser Gly Glu Ser Ile	
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gaa ccc att act gct ttc cag tgt cct acc tgc agg tat gtt atc tcg	192
Glu Pro Ile Thr Ala Phe Gln Cys Pro Thr Cys Arg Tyr Val Ile Ser	
49 54 59 64	
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Leu Asn His Arg Gly Leu Asp Gly Leu Lys Arg Asn Val Thr Leu Gln	
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Asn Ile Ile Asp Arg Phe Gln Lys Ala Ser Val Ser Gly Pro Asn Ser	
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Pro Ser Glu Ser Arg Arg Glu Arg Thr Tyr Arg Pro Thr Thr Ala Met	
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Ser Ser Glu Arg Ile Ala Cys Gln Phe Cys Glu Gln Asp Pro Pro Arg	
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Asp Ala Val Lys Thr Cys Ile Thr Cys Glu Val Ser Tyr Cys Asp Arg	
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Cys Leu Arg Ala Thr His Pro Asn Lys Lys Pro Phe Thr Ser His Arg	
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Asp His Glu Asn Glu Lys Val Asn Met Tyr Cys Val Ser Asp Asp Gln	
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Val Ala Ser Leu Asn Asp Arg Phe Glu Lys Leu Lys Gln Thr Leu Glu	



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cta Leu 513	aag Lys	aag Lys	agc Ser	cac His	acc Thr 518	cca Pro	gag Glu	agg Arg	ttt Phe	agt Ser 523	ggc Gly	aca Thr	ggg Gly	tgc Cys	tat Tyr 528	1584
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atg Met 593	ctg Leu	gtg Val	gat Asp	gtg Val	ccc Pro 598	cca Pro	cac His	ctg Leu	aag Lys	cgt Arg 603	ctg Leu	ggt Gly	gtc Val	ctc Leu	ctg Leu 608	1824
gat Asp 609	tat Tyr	gac Asp	aac Asn	aat Asn	atg Met 614	ctg Leu	tct Ser	ttc Phe	tat Tyr	gac Asp 619	cca Pro	gct Ala	aac Asn	tct Ser	ctc Leu 624	1872
cat His 625	ctt Leu	cat His	act Thr	ttt Phe	gat Asp 630	gtg Val	acc Thr	ttc Phe	att Ile	ctt Leu 635	cca Pro	gtt Val	tgt Cys	cca Pro	aca Thr 640	1920
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cca Pro 657	gat Asp	ttt Phe	att Ile	gat Asp	tac Tyr 662	cct Pro	gag Glu	cgg Arg	cag Gln	gaa Glu 667	tgc Cys	aac Asn	tgc Cys	agg Arg	cct Pro 672	2016









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ccc aag gat gag gcc cag gca tgg gcc cag agt gaa ttt ggg act gaa 974  
Pro Lys Asp Glu Ala Gln Ala Trp Ala Gln Ser Glu Phe Gly Thr Glu  
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Ala Val Ser Gln Ala Glu Gly Val Ser Gln Thr Asn Ala Val Ala Trp  
138 143 148 153





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Lys	Ile	Ala	Met	Gly	Met	Arg	Ser	Ala	Ser	Gln	Phe	Thr	Arg	Asp	Phe	
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Ile	Arg	Asp	Ser	Gly	Val	Val	Ser	Leu	Ile	Glu	Thr	Leu	Leu	Asn	Tyr	
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cca	tcc	tct	aga	gtt	agg	aca	agt	ttt	ttg	gaa	aat	atg	att	cac	atg	2558
Pro	Ser	Ser	Arg	Val	Arg	Thr	Ser	Phe	Leu	Glu	Asn	Met	Ile	His	Met	
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Ala	Pro	Pro	Tyr	Pro	Asn	Leu	Asn	Met	Ile	Glu	Thr	Phe	Ile	Cys	Gln	
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Val	Cys	Glu	Glu	Thr	Leu	Ala	His	Ser	Val	Asp	Ser	Leu	Glu	Gln	Leu	
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Ser	Glu	Asn	Pro	Ala	Val	Ala	Lys	Lys	Leu	Phe	Ser	Ala	Lys	Ala	Leu	
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Ser	Ile	Phe	Val	Gly	Leu	Phe	Asn	Ile	Glu	Glu	Thr	Asn	Asp	Asn	Ile	
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caa	att	gtt	att	aaa	atg	ttt	cag	aat	atc	agt	aac	att	ata	aaa	agt	2942
Gln	Ile	Val	Ile	Lys	Met	Phe	Gln	Asn	Ile	Ser	Asn	Ile	Ile	Lys	Ser	
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gga	aag	atg	tcc	tta	att	gat	gat	gat	ttc	agt	ctt	gag	ccg	ctt	att	2990
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Ser	Ala	Phe	Arg	Glu	Phe	Glu	Glu	Leu	Ala	Lys	Gln	Leu	Gln	Ala	Gln	
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ctggt	887
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Asn	Asp	Thr	Gly	Met	Asn	Ala	Glu	Val	Arg	Tyr	Ser	Ile	Val	Gly	Gly	
703					708					713					718	
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Gln	Met	Ile	Met	Met	Lys	Lys	Lys	Lys	Lys	Lys	Lys	Lys	His	Ser	Pro	
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895					900					905					910	
cta	gaa	gag	caa	aca	atg	gga	aag	tac	aat	tgg	gta	act	aca	cct	act	3623
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Pro Phe Arg Gly Leu Pro Leu Phe Ile His Ser Ile Tyr Ser Trp Ile	
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Asp Thr Leu Ser Thr Arg Pro Gly Tyr Leu Trp Val Val Trp Ile Tyr	
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Arg Asn Leu Ile Gly Ser Val His Phe Phe Phe Ile Leu Thr Leu Ile	
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Val Leu Ile Ile Thr Tyr Leu Tyr Trp Gln Ile Thr Glu Gly Arg Lys	
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Ile Met Ile Arg Leu Leu His Glu Gln Ile Ile Asn Glu Gly Lys Asp	





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Pro Pro His Phe Thr Glu Ser Thr Val Phe Pro Arg Glu Ser Gly Lys	

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246											251											256											261





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Leu Tyr Lys His His Tyr Gln Ala Gly Glu Ser Leu Arg Phe Phe Cys	
714 719 724 729	
tat gag ggc ttt gag ctt atc ggc gag gtc acc atc acc tgt gtg ccc	2319
Tyr Glu Gly Phe Glu Leu Ile Gly Glu Val Thr Ile Thr Cys Val Pro	
730 735 740 745	
ggc cac ccc tcc cag tgg acc agc cag ccc cca ctc tgc aaa gtg acc	2367
Gly His Pro Ser Gln Trp Thr Ser Gln Pro Pro Leu Cys Lys Val Thr	
746 751 756 761	
cag acc aca gat cca tca cgg cag ctg gaa ggg ggg aac ctg gcc ctg	2415
Gln Thr Thr Asp Pro Ser Arg Gln Leu Glu Gly Gly Asn Leu Ala Leu	
762 767 772 777	
gcc atc ctg ctg cct cta ggc ttg gtc att gtc ctc ggc agt ggc gtt	2463
Ala Ile Leu Leu Pro Leu Gly Leu Val Ile Val Leu Gly Ser Gly Val	
778 783 788 793	
tac atc tac tac acc aag ctt cag gga aag tcc ctt ttc ggc ttc tcg	2511
Tyr Ile Tyr Tyr Thr Lys Leu Gln Gly Lys Ser Leu Phe Gly Phe Ser	
794 799 804 809	
ggc tcc cac tcc tac agc ccc atc acc gtg gag tcg gac ttc agc aac	2559
Gly Ser His Ser Tyr Ser Pro Ile Thr Val Glu Ser Asp Phe Ser Asn	
810 815 820 825	
ccg ctg tat gaa gct ggg gat acg cgg gag tat gaa gtt tcc atc tga	2607
Pro Leu Tyr Glu Ala Gly Asp Thr Arg Glu Tyr Glu Val Ser Ile *	
826 831 836 841	
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3159

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1 5

ccg cct ccc cag ctg ctg ttc cta att ctg ctg agc tgt ccc tgg atc 159  
Pro Pro Pro Gln Leu Leu Phe Leu Ile Leu Leu Ser Cys Pro Trp Ile  
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cag ggt ctg ccc ctg aag gag gag gag ata ttg cca gag cct gga agt 207  
Gln Gly Leu Pro Leu Lys Glu Glu Glu Ile Leu Pro Glu Pro Gly Ser  
26 31 36 41

gag acc ccc acg gtg gcc tct gag gcc ctg gct gaa ctg ctt cat ggg 255  
Glu Thr Pro Thr Val Ala Ser Glu Ala Leu Ala Glu Leu Leu His Gly  
42 47 52 57

gcc ctg ctg agg agg ggc cca gag atg ggc tac ctg cca ggg cct ccc 303  
Ala Leu Leu Arg Arg Gly Pro Glu Met Gly Tyr Leu Pro Gly Pro Pro  
58 63 68 73

ctt ggg cct gag gga gga gag gag gag acg acg acc acc atc atc acc 351  
Leu Gly Pro Glu Gly Gly Glu Glu Glu Thr Thr Thr Thr Ile Ile Thr  
74 79 84 89

acg aca act gtt acc act acg gtg acc agc cca gtt ctg tgt aat aac 399  
Thr Thr Thr Val Thr Thr Thr Val Thr Ser Pro Val Leu Cys Asn Asn  
90 95 100 105

aac atc tcc gag ggc gaa ggg tat gtg gag tct cca gat ctg ggg agc 447  
Asn Ile Ser Glu Gly Glu Gly Tyr Val Glu Ser Pro Asp Leu Gly Ser  
106 111 116 121

ccc gtc agc cgc acc ctg ggg ctc ctg gac tgc act tac agc atc cat 495  
Pro Val Ser Arg Thr Leu Gly Leu Leu Asp Cys Thr Tyr Ser Ile His  
122 127 132 137

gtc tac cct ggc tac ggc att gag atc cag gtg cag acg ctg aac ctg 543  
Val Tyr Pro Gly Tyr Gly Ile Glu Ile Gln Val Gln Thr Leu Asn Leu  
138 143 148 153



Asn 378	Pro	Leu	Leu	Leu	Ser 383	Leu	Arg	Phe	Glu	Ala 388	Phe	Glu	Glu	Asp	Arg 393	
tgc 394	ttc	gcc	ccc	ttc	ctg	gca	cat	gga	aat	gtc	act	acc	acg	gac	cct	1311
Cys	Phe	Ala	Pro	Phe	Leu 399	Ala	His	Gly	Asn	Val 404	Thr	Thr	Thr	Asp	Pro 409	
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Glu	Tyr	Arg	Pro	Gly	Ala 415	Leu	Ala	Thr	Phe	Ser 420	Cys	Leu	Pro	Gly	Tyr 425	
gcc 426	ctg	gag	ccc	cct	ggg	ccc	ccc	aat	gcc	atc	gaa	tgt	gtg	gat	ccc	1407
Ala	Leu	Glu	Pro	Pro	Gly 431	Pro	Pro	Asn	Ala	Ile 436	Glu	Cys	Val	Asp	Pro 441	
aca 442	gaa	ccc	cac	tgg	aac	gac	aca	gag	ccg	gcc	tgc	aaa	gcc	atg	tgt	1455
Thr	Glu	Pro	His	Trp	Asn 447	Asp	Thr	Glu	Pro	Ala 452	Cys	Lys	Ala	Met	Cys 457	
gga 458	ggg	gag	ctg	tcg	gaa	cca	gct	ggc	gtg	gtc	ctc	tct	ccc	gac	tgg	1503
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ccc 474	cag	agc	tat	agc	ccg	ggc	caa	gac	tgc	gtg	tgg	ggc	gtg	cac	gtc	1551
Pro	Gln	Ser	Tyr	Ser	Pro 479	Gly	Gln	Asp	Cys	Val 484	Trp	Gly	Val	His	Val 489	
cag 490	gaa	gag	aag	cgc	atc	ttg	ctc	caa	gtt	gag	ata	ttg	aat	gtg	cgg	1599
Gln	Glu	Glu	Lys	Arg	Ile 495	Leu	Leu	Gln	Val	Glu 500	Ile	Leu	Asn	Val	Arg 505	
gaa 506	ggg	gac	atg	ctg	acg	ctg	ttt	gac	ggg	gac	ggg	ccc	agc	gcc	cga	1647
Glu	Gly	Asp	Met	Leu	Thr 511	Leu	Phe	Asp	Gly	Asp 516	Gly	Pro	Ser	Ala	Arg 521	
gtc 522	ttg	gcc	cag	ctg	cgg	gga	cct	cag	ccg	cgc	cgc	cgc	ctt	ctc	tcc	1695
Val	Leu	Ala	Gln	Leu	Arg 527	Gly	Pro	Gln	Pro	Arg 532	Arg	Arg	Leu	Leu	Ser 537	
tct 538	ggg	ccc	gac	ctc	aca	ctg	cag	ttt	cag	gca	ccg	ccc	ggg	ccc	cca	1743
Ser	Gly	Pro	Asp	Leu	Thr 543	Leu	Gln	Phe	Gln	Ala 548	Pro	Pro	Gly	Pro	Pro 553	
aat 554	cca	ggc	ctg	ggc	cag	ggc	ttc	gta	ttg	cac	ttc	aaa	gag	gtc	ccg	1791
Asn	Pro	Gly	Leu	Gly	Gln 559	Gly	Phe	Val	Leu	His 564	Phe	Lys	Glu	Val	Pro 569	
agg 570	aac	gac	acg	tgc	ccc	gag	ctg	cca	cct	ccg	gag	tgg	ggc	tgg	aga	1839
Arg	Asn	Asp	Thr	Cys	Pro 575	Glu	Leu	Pro	Pro	Pro 580	Glu	Trp	Gly	Trp	Arg 585	
acg 586	gca	tcc	cac	ggg	gac	ctg	atc	cgg	ggc	acg	gtg	ctc	acc	tac	cag	1887
Thr	Ala	Ser	His	Gly	Asp 591	Leu	Ile	Arg	Gly	Thr 596	Val	Leu	Thr	Tyr	Gln 601	
tgc 601	gag	cct	ggc	tac	gag	ctg	cta	ggc	tcc	gac	att	ctc	act	tgc	cag	1935
Cys	Glu	Pro	Gly	Tyr	Glu	Leu	Leu	Gly	Ser	Asp	Ile	Leu	Thr	Cys	Gln	



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 Glu Ala Gly Asp Thr Arg Glu Tyr Glu Val Ser Ile \*  
 842 847 852  
  
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 cgaggggggct ttgatggccc tggagatcct acagtaaata aaccagcatc ctgccgcca 2836  
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 ccggcttctc agcaccccg c aaccggcacc ggcgctgtcc agaccgaggc c atg aag 177  
 Met Lys  
 1  
  
 cag att ctc ggg gtg atc gac aag aaa ctt cgg aac ctg gag aag aaa 225  
 Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys  
 3 8 13 18  
  
 aag ggt aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg 273  
 Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg  
 19 24 29 34  
  
 ctt aat caa gat cag ctg gat gcc gtt tct aag tac cag gaa gtc aca 321  
 Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr  
 35 40 45 50





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Gln	Gln	Gln	Pro	Gln	Ala	Ala	Ser	Pro	Ser	Val	Pro	Glu	Pro	His	Ser	
275					280					285					290	
ttg	act	cca	gtg	gct	cag	gca	gat	ccc	ctt	gtg	aga	aga	cag	cga	gta	1089
Leu	Thr	Pro	Val	Ala	Gln	Ala	Asp	Pro	Leu	Val	Arg	Arg	Gln	Arg	Val	
291					296					301					306	
caa	gac	ctt	atg	gca	caa	atg	cag	ggg	ccc	gat	aat	ttc	ata	cag	gat	1137
Gln	Asp	Leu	Met	Ala	Gln	Met	Gln	Gly	Pro	Asp	Asn	Phe	Ile	Gln	Asp	
307					312					317					322	
tca	atg	ctg	gat	ttt	gaa	aat	cag	aca	ctt	gat	cct	gcc	att	gta	tct	1185
Ser	Met	Leu	Asp	Phe	Glu	Asn	Gln	Thr	Leu	Asp	Pro	Ala	Ile	Val	Ser	
323					328					333					338	
gca	cag	cct	atg	aat	cca	aca	caa	aac	atg	gac	atg	ccc	cag	ctg	gtt	1233
Ala	Gln	Pro	Met	Asn	Pro	Thr	Gln	Asn	Met	Asp	Met	Pro	Gln	Leu	Val	
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tgc	cct	cca	gtt	cat	tct	gaa	tct	aga	ctt	gct	cag	cct	aat	caa	gtt	1281
Cys	Pro	Pro	Val	His	Ser	Glu	Ser	Arg	Leu	Ala	Gln	Pro	Asn	Gln	Val	
355					360					365					370	
cct	gta	caa	cca	gaa	gcg	aca	cag	gtt	cct	ttg	gta	tca	tcc	aca	agt	1329
Pro	Val	Gln	Pro	Glu	Ala	Thr	Gln	Val	Pro	Leu	Val	Ser	Ser	Thr	Ser	
371					376					381					386	
gag	ggg	tac	aca	gca	tct	caa	ccc	ttg	tac	cag	cct	tct	cat	gct	aca	1377
Glu	Gly	Tyr	Thr	Ala	Ser	Gln	Pro	Leu	Tyr	Gln	Pro	Ser	His	Ala	Thr	
387					392					397					402	
gag	caa	cga	cca	cag	aag	gaa	cca	att	gat	cag	att	cag	gca	aca	atc	1425
Glu	Gln	Arg	Pro	Gln	Lys	Glu	Pro	Ile	Asp	Gln	Ile	Gln	Ala	Thr	Ile	
403					408					413					418	
tct	tta	aat	aca	gac	cag	act	aca	gca	tca	tca	tcc	ctt	cct	gct	gcg	1473
Ser	Leu	Asn	Thr	Asp	Gln	Thr	Thr	Ala	Ser	Ser	Ser	Leu	Pro	Ala	Ala	
419					424					429					434	
tct	cag	cct	caa	gta	ttt	cag	gct	ggg	aca	agc	aaa	cct	tta	cat	agc	1521
Ser	Gln	Pro	Gln	Val	Phe	Gln	Ala	Gly	Thr	Ser	Lys	Pro	Leu	His	Ser	
435					440					445					450	
agt	gga	atc	aat	gta	aat	gca	gct	cca	ttc	caa	tcc	atg	caa	acg	gtg	1569
Ser	Gly	Ile	Asn	Val	Asn	Ala	Ala	Pro	Phe	Gln	Ser	Met	Gln	Thr	Val	
451					456					461					466	
ttc	aat	atg	aat	gcc	cca	gtt	cct	cct	gtt	aat	gaa	cca	gaa	act	tta	1617
Phe	Asn	Met	Asn	Ala	Pro	Val	Pro	Pro	Val	Asn	Glu	Pro	Glu	Thr	Leu	
467					472					477					482	
aaa	cag	caa	aat	cag	tac	cag	gcc	agt	tat	aac	cag	agc	ttt	tct	agt	1665
Lys	Gln	Gln	Asn	Gln	Tyr	Gln	Ala	Ser	Tyr	Asn	Gln	Ser	Phe	Ser	Ser	
483					488					493					498	
cag	cct	cac	caa	gta	gaa	caa	aca	gag	ctt	cag	caa	gaa	cag	ctt	caa	1713



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 ctt cag aat tct gtg tta gct gaa gat ggg gaa gta aga tca agt tgt 94  
 Leu Gln Asn Ser Val Leu Ala Glu Asp Gly Glu Val Arg Ser Ser Cys  
 16 21 26 31  
 cgt act gct ccg aca gat tta gtt ttc atc tta gat ggc tct tat agt 142  
 Arg Thr Ala Pro Thr Asp Leu Val Phe Ile Leu Asp Gly Ser Tyr Ser  
 32 37 42 47  
 gtt ggc cca gaa aac ttt gaa ata gtg aaa aag tgg ctt gtc aat atc 190  
 Val Gly Pro Glu Asn Phe Glu Ile Val Lys Lys Trp Leu Val Asn Ile  
 48 53 58 63  
 aca aaa aac ttt gac ata ggg ccg aag ttt att caa gtt gga gtg gtt 238  
 Thr Lys Asn Phe Asp Ile Gly Pro Lys Phe Ile Gln Val Gly Val Val  
 64 69 74 79  
 caa tat agt gac tac cct gtg ctg gag att cct ctc gga agc tat gat 286  
 Gln Tyr Ser Asp Tyr Pro Val Leu Glu Ile Pro Leu Gly Ser Tyr Asp  
 80 85 90 95





544	549	554	559	
ggc aaa aag gga agt ata gat cac aca aca aag tat tca tat tga act				1726
Gly Lys Lys Gly Ser Ile Asp His Thr Thr Lys Tyr Ser Tyr *				
560	565	570		

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cctgaagcgg agccgccgtc gccaccagcg ccgtc	
atg tcg gcc ccc gcc ggg	173
Met Ser Ala Pro Ala Gly	
1	

tcc tct cac ccg gcc gcc agc gcc cgg atc ccg ccc aag ttc ggc gga	221
Ser Ser His Pro Ala Ala Ser Ala Arg Ile Pro Pro Lys Phe Gly Gly	
7 12 17 22	

tcg gcc gtc tca gga gcc gca gcg ccc gcg ggc ccg ggt gcg ggc ccg	269
Ser Ala Val Ser Gly Ala Ala Ala Pro Ala Gly Pro Gly Ala Gly Pro	
23 28 33 38	

gcg ccg cac cag cag aac ggt cca gcc cag aat caa atg cag gtt cca	317
Ala Pro His Gln Gln Asn Gly Pro Ala Gln Asn Gln Met Gln Val Pro	
39 44 49 54	

tct gga tat gga ttg cat cat caa aac tat att gct ccc tca gga cat	365
Ser Gly Tyr Gly Leu His His Gln Asn Tyr Ile Ala Pro Ser Gly His	
55 60 65 70	

tac tct caa gga cct ggg aaa atg acc tca ttg cca ttg gat acc cag	413
Tyr Ser Gln Gly Pro Gly Lys Met Thr Ser Leu Pro Leu Asp Thr Gln	
71 76 81 86	

tgt ggt gat tac tac tct gct ctc tat aca gta cca aca caa aat gtg	461
Cys Gly Asp Tyr Tyr Ser Ala Leu Tyr Thr Val Pro Thr Gln Asn Val	
87 92 97 102	

act cct aac aca gtg aac cag caa cca gga gca cag cag ttg tac agc	509
Thr Pro Asn Thr Val Asn Gln Gln Pro Gly Ala Gln Gln Leu Tyr Ser	









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cgt 807	gtg Val	tct Ser	gta Val	ttt Phe	cag Gln 812	aca Thr	cag Gln	tta Leu	cct Pro	tcc Ser 817	ttg Leu	ggg Gly	gca Ala	gga Gly	ctt Leu 822	2621
ctg 823	caa Gln	tcc Ser	aga Arg	gaa Glu	gat Asp 828	cct Pro	aat Asn	cag Gln	aga Arg	tca Ser 833	agt Ser	aca Thr	aag Lys	gtg Val	gta Val 838	2669
caa 839	cat His	ctt Leu	ggc Gly	cct Pro	gca Ala 844	act Thr	gat Asp	ttt Phe	tat Tyr	aag Lys 849	aaa Lys	ctt Leu	gca Ala	tta Leu	gat Asp 854	2717
tgc 855	tcg Ser	gga Gly	cag Gln	caa Gln	act Thr 860	gca Ala	gtg Val	gat Asp	ttg Leu	ttc Phe 865	ctt Leu	tta Leu	agt Ser	tca Ser	cag Gln 870	2765
tat 871	tct Ser	gat Asp	ctt Leu	gct Ala	tct Ser 876	cta Leu	gct Ala	tgc Cys	atg Met	tcc Ser 881	aag Lys	tat Tyr	tct Ser	gca Ala	ggg Gly 886	2813
tgc 887	atc Ile	tat Tyr	tat Tyr	tat Tyr	cca Pro 892	tca Ser	ttc Phe	cac His	tat Tyr	act Thr 897	cac His	aat Asn	cct Pro	tca Ser	caa Gln 902	2861
gca 903	gaa Glu	aag Lys	tta Leu	caa Gln	aaa Lys 908	gac Asp	cta Leu	aaa Lys	cgg Arg	tat Tyr 913	ctc Leu	aca Thr	aga Arg	aaa Lys	att Ile 918	2909
ggg 919	ttt Phe	gaa Glu	gct Ala	gtt Val	atg Met 924	aga Arg	ata Ile	agg Arg	tgt Cys	act Thr 929	aaa Lys	ggg Gly	ctt Leu	tca Ser	atg Met 934	2957
cac 935	act Thr	ttt Phe	cac His	ggg Gly	aac Asn 940	ttc Phe	ttt Phe	gtc Val	cgt Arg	tct Ser 945	act Thr	gat Asp	ttg Leu	tta Leu	tcc Ser 950	3005
ctt 951	gcc Ala	aac Asn	atc Ile	aat Asn	cct Pro 956	gat Asp	gct Ala	gga Gly	ttt Phe	gcg Ala 961	gtg Val	cag Gln	ttg Leu	tca Ser	att Ile 966	3053
gaa 967	gaa Glu	agt Ser	tta Leu	aca Thr	gat Asp 972	act Thr	tcc Ser	tta Leu	gta Val	tgt Cys 977	ttt Phe	caa Gln	aca Thr	gcc Ala	cta Leu 982	3101
tta 983	tat Tyr	aca Thr	tca Ser	agc Ser	aaa Lys 988	ggg Gly	gag Glu	cgg Arg	aga Arg	att Ile 993	aga Arg	gta Val	cat His	aca Thr	ctt Leu 998	3149
tgt 999	ttg Leu	cca Pro	gtg Val	gta Val	agt Ser 1004	tca Ser	cta Leu	gca Ala	gat Asp	gta Val 1009	tat Tyr	gcg Ala	gga Gly	gtg Val	gat Asp 1014	3197
gta Val	caa Gln	gct Ala	gcc Ala	atc Ile	tgc Cys	ctt Leu	ctg Leu	gca Ala	aac Asn	atg Met	gct Ala	gtg Val	gat Asp	cgg Arg	tcc Ser	3245

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Val Ser Ser Ser Leu Ser Asp Ala Arg Asp Ala Leu Val Asn Ala Val							
1031		1036		1041		1046	
gtg gac tca ttg tct gca tat ggc tca act gtc tca aat tta cag cac							3341
Val Asp Ser Leu Ser Ala Tyr Gly Ser Thr Val Ser Asn Leu Gln His							
1047		1052		1057		1062	
tct gca ttg atg gcg ccc agc tcc ctc aag ttg ttt cct ctc tat gtt							3389
Ser Ala Leu Met Ala Pro Ser Ser Leu Lys Leu Phe Pro Leu Tyr Val							
1063		1068		1073		1078	
ttg gcc ctt ctc aaa cag aaa gca ttt aga acg ggt aca agc aca cgg							3437
Leu Ala Leu Leu Lys Gln Lys Ala Phe Arg Thr Gly Thr Ser Thr Arg							
1079		1084		1089		1094	
ctg gat gat cgt gta tat gcc atg tgt cag ata aag tct cag cca ctt							3485
Leu Asp Asp Arg Val Tyr Ala Met Cys Gln Ile Lys Ser Gln Pro Leu							
1095		1100		1105		1110	
gtt cat cta atg aaa atg att cat ccc aac tta tac agg ata gac aga							3533
Val His Leu Met Lys Met Ile His Pro Asn Leu Tyr Arg Ile Asp Arg							
1111		1116		1121		1126	
ttg aca gat gag ggt gca gta cat gtt aat gac agg att gta cca cag							3581
Leu Thr Asp Glu Gly Ala Val His Val Asn Asp Arg Ile Val Pro Gln							
1127		1132		1137		1142	
cca cct ctt caa aaa ttg tct gca gag aag ctg aca aga gaa ggt gct							3629
Pro Pro Leu Gln Lys Leu Ser Ala Glu Lys Leu Thr Arg Glu Gly Ala							
1143		1148		1153		1158	
ttc ctt atg gac tgt ggc tct gtt ttt tac att tgg gtt ggg aaa ggc							3677
Phe Leu Met Asp Cys Gly Ser Val Phe Tyr Ile Trp Val Gly Lys Gly							
1159		1164		1169		1174	
tgt gac aat aac ttc ata gag gat gtg ctt gga tat act aat ttt gca							3725
Cys Asp Asn Asn Phe Ile Glu Asp Val Leu Gly Tyr Thr Asn Phe Ala							
1175		1180		1185		1190	
tca ata cca cag aaa atg aca cat ctt cca gag cta gat aca ctt tca							3773
Ser Ile Pro Gln Lys Met Thr His Leu Pro Glu Leu Asp Thr Leu Ser							
1191		1196		1201		1206	
tca gaa aga gcc aga tcc ttc ata act tgg ctt aga gac agc aga cca							3821
Ser Glu Arg Ala Arg Ser Phe Ile Thr Trp Leu Arg Asp Ser Arg Pro							
1207		1212		1217		1222	
tta agt cca atc ctt cac ata gta aaa gat gag agt cct gcc aaa gca							3869
Leu Ser Pro Ile Leu His Ile Val Lys Asp Glu Ser Pro Ala Lys Ala							
1223		1228		1233		1238	
gaa ttt ttt cag cat ttg att gaa gac cgg aca gag gct gca ttt tct							3917
Glu Phe Phe Gln His Leu Ile Glu Asp Arg Thr Glu Ala Ala Phe Ser							
1239		1244		1249		1254	



ttccgcccgc tccagctt	atg gaa act ggt caa aga act cat gca agt gga	411
	Met Glu Thr Gly Gln Arg Thr His Ala Ser Gly	
	1 5	
act tac agc ttc ctt gat cgg act cag cat tca gat atc aaa gca gac	459	
Thr Tyr Ser Phe Leu Asp Arg Thr Gln His Ser Asp Ile Lys Ala Asp		
12 17 22 27		
tgc aat acc tgc gtg gaa ata gaa gac aga aag gtt tca aga caa cag	507	
Cys Asn Thr Cys Val Glu Ile Glu Asp Arg Lys Val Ser Arg Gln Gln		
28 33 38 43		
atg aat tgt gaa aga gag cag cta agg ggt aat cag gaa gca gcc gct	555	
Met Asn Cys Glu Arg Glu Gln Leu Arg Gly Asn Gln Glu Ala Ala Ala		
44 49 54 59		
gcc cct gac aca atg gct cag cct tac gct tcg gcc cag ttt gct ccc	603	
Ala Pro Asp Thr Met Ala Gln Pro Tyr Ala Ser Ala Gln Phe Ala Pro		
60 65 70 75		
ccg cag aac ggt atc ccc gcg gaa tac acg gcc cct cat ccc cac ccc	651	
Pro Gln Asn Gly Ile Pro Ala Glu Tyr Thr Ala Pro His Pro His Pro		
76 81 86 91		
gcg cca gag tac aca ggc cag acc acg gtt ccc gag cac aca tta aac	699	
Ala Pro Glu Tyr Thr Gly Gln Thr Thr Val Pro Glu His Thr Leu Asn		
92 97 102 107		
ctg tac cct ccc gcc cag acg cac tcc gag cag agc ccg gcg gac acg	747	
Leu Tyr Pro Pro Ala Gln Thr His Ser Glu Gln Ser Pro Ala Asp Thr		
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Ser Ala Gln Thr Val Ser Gly Thr Ala Thr Gln Thr Asp Asp Ala Ala		
124 129 134 139		
ccg acg gat ggc cag ccc cag aca caa cct tct gaa aac acg gaa aac	843	
Pro Thr Asp Gly Gln Pro Gln Thr Gln Pro Ser Glu Asn Thr Glu Asn		
140 145 150 155		
aag tct cag ccc aag cgg ctg cat gtc tcc aat atc ccc ttc agg ttc	891	
Lys Ser Gln Pro Lys Arg Leu His Val Ser Asn Ile Pro Phe Arg Phe		
156 161 166 171		
cgg gat ccg gac ctc aga caa atg ttt ggt caa ttt ggt aaa atc tta	939	
Arg Asp Pro Asp Leu Arg Gln Met Phe Gly Gln Phe Gly Lys Ile Leu		
172 177 182 187		
gat gtt gaa att att ttt aat gag cga ggc tca aag gga ttt ggt ttc	987	
Asp Val Glu Ile Ile Phe Asn Glu Arg Gly Ser Lys Gly Phe Gly Phe		
188 193 198 203		
gta act ttc gaa aat agt gcc gat gcg gac agg gcg agg gag aaa tta	1035	
Val Thr Phe Glu Asn Ser Ala Asp Ala Asp Arg Ala Arg Glu Lys Leu		
204 209 214 219		

cac ggc acc gtg gta gag ggc cgt aaa atc gag gta aat aat gcc aca	1083
His Gly Thr Val Val Glu Gly Arg Lys Ile Glu Val Asn Asn Ala Thr	
220 225 230 235	
gca cgt gta atg aca aat aaa aag acc gtc aac cct tat aca aat ggc	1131
Ala Arg Val Met Thr Asn Lys Lys Thr Val Asn Pro Tyr Thr Asn Gly	
236 241 246 251	
tgg aaa ttg aat cca gtt gtg ggt gca gtc tac agt ccc gaa ttc tat	1179
Trp Lys Leu Asn Pro Val Val Gly Ala Val Tyr Ser Pro Glu Phe Tyr	
252 257 262 267	
gca ggc acg gtc ctg ttg tgc cag gcc aac cag gag gga tct tcc atg	1227
Ala Gly Thr Val Leu Leu Cys Gln Ala Asn Gln Glu Gly Ser Ser Met	
268 273 278 283	
tac agt gcc ccc agt tca ctt gta tat act tct gca atg cca ggc ttc	1275
Tyr Ser Ala Pro Ser Ser Leu Val Tyr Thr Ser Ala Met Pro Gly Phe	
284 289 294 299	
ccg tat cca gca gcc acc gcc gcg gcc gcc tac cga ggg gcg cac ctg	1323
Pro Tyr Pro Ala Ala Thr Ala Ala Ala Ala Tyr Arg Gly Ala His Leu	
300 305 310 315	
cga ggc cgc ggt cgc acc gtg tac aac acc ttc agg gcc gcg gcg ccc	1371
Arg Gly Arg Gly Arg Thr Val Tyr Asn Thr Phe Arg Ala Ala Ala Pro	
316 321 326 331	
ccg ccc ccg atc ccg gcc tac ggc ggt gtt gtt tac cag gat gga ttt	1419
Pro Pro Pro Ile Pro Ala Tyr Gly Gly Val Val Tyr Gln Asp Gly Phe	
332 337 342 347	
tat ggt gca gac att tat ggt ggt tat gct gca tac cgc tac gcc cag	1467
Tyr Gly Ala Asp Ile Tyr Gly Gly Tyr Ala Ala Tyr Arg Tyr Ala Gln	
348 353 358 363	
cct acc cct gcc act gcc gct gcc tac agt gac agt tac gga cga gtt	1515
Pro Thr Pro Ala Thr Ala Ala Ala Tyr Ser Asp Ser Tyr Gly Arg Val	
364 369 374 379	
tat gct gcc gac ccc tac cac cac gca ctt gct cca gcc ccc acc tac	1563
Tyr Ala Ala Asp Pro Tyr His His Ala Leu Ala Pro Ala Pro Thr Tyr	
380 385 390 395	
ggc gtt ggt gcc atg aat gct ttt gca cct ttg act gat gcc aag act	1611
Gly Val Gly Ala Met Asn Ala Phe Ala Pro Leu Thr Asp Ala Lys Thr	
396 401 406 411	
agg agc cat gct gat gat gtg ggt ctc gtt ctt tct tca ttg cag gct	1659
Arg Ser His Ala Asp Asp Val Gly Leu Val Leu Ser Ser Leu Gln Ala	
412 417 422 427	
agt ata tac cga ggg gga tac aac cgt ttt gct cca tac taa atgacaa	1708
Ser Ile Tyr Arg Gly Gly Tyr Asn Arg Phe Ala Pro Tyr *	
428 433 438	
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tacatgcagt agtacatcat tttagcaact ct

1800

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<222> (27) .. (2267)

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1 5

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Met Glu Glu Val Met Gln Lys Asp Gln Lys Lys Val Pro Gln Lys Lys  
10 15 20 25

gtt cct tat gca aaa ccc att cct gct cag ttc cag cag gct tgg atg 149  
Val Pro Tyr Ala Lys Pro Ile Pro Ala Gln Phe Gln Gln Ala Trp Met  
26 31 36 41

caa aat aaa gtt cca att cct gct cca aat gag gtg ctg aat gac aga 197  
Gln Asn Lys Val Pro Ile Pro Ala Pro Asn Glu Val Leu Asn Asp Arg  
42 47 52 57

aaa gaa gac att aaa ttg gaa gag aag aaa aaa aca caa gca gaa att 245  
Lys Glu Asp Ile Lys Leu Glu Glu Lys Lys Lys Thr Gln Ala Glu Ile  
58 63 68 73

gag caa gaa atg gct aca tta caa tat act aac cca caa ctt ctg gag 293  
Glu Gln Glu Met Ala Thr Leu Gln Tyr Thr Asn Pro Gln Leu Leu Glu  
74 79 84 89

caa ctt aaa att gaa aga ctt gca cag aaa caa gtt gag caa att cag 341  
Gln Leu Lys Ile Glu Arg Leu Ala Gln Lys Gln Val Glu Gln Ile Gln  
90 95 100 105

cct cct ccc tca tct ggc acc cct ctc ctc gga ccc cag cct ttt cca 389  
Pro Pro Pro Ser Ser Gly Thr Pro Leu Leu Gly Pro Gln Pro Phe Pro  
106 111 116 121

gga caa ggt cca atg tct cag att cct caa ggt ttt caa cag ccc cat 437  
Gly Gln Gly Pro Met Ser Gln Ile Pro Gln Gly Phe Gln Gln Pro His  
122 127 132 137

cca tct cag cag atg cca atg aac atg gct caa atg ggg cct cca ggt 485  
Pro Ser Gln Gln Met Pro Met Asn Met Ala Gln Met Gly Pro Pro Gly  
138 143 148 153

cca cag gga cag ttt agg cct cct gga ccc cag gga caa atg gga cca 533







aag cgc ccc tgg cat gat ggc cca ggc act tct gag cac aga gag atg	1925
Lys Arg Pro Trp His Asp Gly Pro Gly Thr Ser Glu His Arg Glu Met	
618 623 628 633	
gag gcc cca gga ggc cct tct gaa gac cga gga ggc aaa ggc cga ggg	1973
Glu Ala Pro Gly Gly Pro Ser Glu Asp Arg Gly Gly Lys Gly Arg Gly	
634 639 644 649	
ggc cca gga cct gct cag aga gtg ccc aaa tct ggg cgt tcc agc tcc	2021
Gly Pro Gly Pro Ala Gln Arg Val Pro Lys Ser Gly Arg Ser Ser Ser	
650 655 660 665	
tta gac gga gag cac cac gat gga tac cac aga gat gaa cct ttt ggg	2069
Leu Asp Gly Glu His His Asp Gly Tyr His Arg Asp Glu Pro Phe Gly	
666 671 676 681	
ggc cct cca ggc agt ggc acc cct tct cga ggg ggc cgg agt ggc agt	2117
Gly Pro Pro Gly Ser Gly Thr Pro Ser Arg Gly Gly Arg Ser Gly Ser	
682 687 692 697	
aac tgg ggt aga ggg agt aac atg aac tct ggc ccg ccg agg cga gga	2165
Asn Trp Gly Arg Gly Ser Asn Met Asn Ser Gly Pro Pro Arg Arg Gly	
698 703 708 713	
gct ttc ctg ggt ggt ggg agg ggt ccg gta aaa cct cga act gag ttc	2213
Ala Phe Leu Gly Gly Gly Arg Gly Pro Val Lys Pro Arg Thr Glu Phe	
714 719 724 729	
cct gag ggc gtt ttt gga cag att gta aga act ttt ggt gga ctt cac	2261
Pro Glu Gly Val Phe Gly Gln Ile Val Arg Thr Phe Gly Gly Leu His	
730 735 740 745	
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Pro *	
746	

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agcgttgcca acgtgtacgg agatagccga agaggcggaa gcggggccac aagagccctt	180

cctgcagggga acctcagggt tcagagagcc gaaaagttgg gaggcgtaac cacttacagg	240
ccggaagtgt ccgggggtgga cgcattcggg tagccgaaga agtcccagga ttgccgaaga	300
agtcccagga tttccgaagc gagccgaagc atcgcgacag ttttcagaga cagctgatcg	360
gttggagctg ttgcgccgag cagtc atg gcg gcg gcc aga gct act acg ccg	412
Met Ala Ala Ala Arg Ala Thr Thr Pro	
1 5	
gcc gat ggc gag gag ccc gcc ccg gag gct gag gct ctg gcc gca gcc	460
Ala Asp Gly Glu Glu Pro Ala Pro Glu Ala Glu Ala Leu Ala Ala Ala	
10 15 20 25	
cgg gag cgg agc agc cgc ttc ttg agc ggc ctg gag ctg gtg aag cag	508
Arg Glu Arg Ser Ser Arg Phe Leu Ser Gly Leu Glu Leu Val Lys Gln	
26 31 36 41	
ggc gcc gag gcg cgc gtg ttc cgt ggc cgc ttc cag ggc cgc gcg gcg	556
Gly Ala Glu Ala Arg Val Phe Arg Gly Arg Phe Gln Gly Arg Ala Ala	
42 47 52 57	
gtg atc aag cac cgc ttc ccc aag ggc tac cgg cac ccg gcg ctg gag	604
Val Ile Lys His Arg Phe Pro Lys Gly Tyr Arg His Pro Ala Leu Glu	
58 63 68 73	
gcg cgg ctt ggc aga cgg cgg acg gtg cag gag gcc cgg gcg ctc ctc	652
Ala Arg Leu Gly Arg Arg Arg Thr Val Gln Glu Ala Arg Ala Leu Leu	
74 79 84 89	
cgc tgt cgc cgc gct gga ata tct gcc cca gtt gtc ttt ttt gtg gac	700
Arg Cys Arg Arg Ala Gly Ile Ser Ala Pro Val Val Phe Phe Val Asp	
90 95 100 105	
tat gct tcc aac tgc tta tat atg gaa gaa att gaa ggc tca gtg act	748
Tyr Ala Ser Asn Cys Leu Tyr Met Glu Glu Ile Glu Gly Ser Val Thr	
106 111 116 121	
gtt cga gat tat att cag tcc act atg gag act gaa aaa act ccc cag	796
Val Arg Asp Tyr Ile Gln Ser Thr Met Glu Thr Glu Lys Thr Pro Gln	
122 127 132 137	
ggc ctc tcc aac tta gcc aag aca att ggg cag gtt ttg gct cga atg	844
Gly Leu Ser Asn Leu Ala Lys Thr Ile Gly Gln Val Leu Ala Arg Met	
138 143 148 153	
cac gat gaa gac ctc att cat ggt gat ctc acc acc tcc aac atg ctc	892
His Asp Glu Asp Leu Ile His Gly Asp Leu Thr Thr Ser Asn Met Leu	
154 159 164 169	
ctg aaa ccc ccc ctg gaa cag ctg aac att gtg ctc ata gac ttt ggg	940
Leu Lys Pro Pro Leu Glu Gln Leu Asn Ile Val Leu Ile Asp Phe Gly	
170 175 180 185	
ctg agt ttc att tca gca ctt cca gag gat aag gga gta gac ctc tat	988
Leu Ser Phe Ile Ser Ala Leu Pro Glu Asp Lys Gly Val Asp Leu Tyr	
186 191 196 201	

gtc ctg gag aag gcc ttc ctc agt acc cat ccc aac act gaa act gtg	1036
Val Leu Glu Lys Ala Phe Leu Ser Thr His Pro Asn Thr Glu Thr Val	
202 207 212 217	
ttt gaa gcc ttt ctg aag agc tac tcc acc tcc tcc aaa aag gcc agg	1084
Phe Glu Ala Phe Leu Lys Ser Tyr Ser Thr Ser Ser Lys Lys Ala Arg	
218 223 228 233	
cca gtg cta aaa aaa tta gat gaa gtg cgc ctg aga gga aga aag agg	1132
Pro Val Leu Lys Lys Leu Asp Glu Val Arg Leu Arg Gly Arg Lys Arg	
234 239 244 249	
tcc atg gtt ggg tag aagaatgtgt atgacaacca cacacagtga agctcttttt	1187
Ser Met Val Gly *	
250	
tcaaagtaaa tttgaagaaa tgctacaagt atgagatgag atctaagtaa aggtgttaag	1247
atattttttaa aaaaaaaaaa	1267

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 <212> DNA  
 <213> Homo sapiens  
  
 <220>  
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 <222> (218)..(1399)

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gggtcaaagac tgggtgcctg ggagctgagg cagccaccgt ttcagcctgg ccagccctct	180
ggacccccgag gttggaccct actgtgacac acctacc atg cgg aca ctc ttc aac	235
Met Arg Thr Leu Phe Asn	
1	
ctc ctc tgg ctt gcc ctg gcc tgc agc cct gtt cac act acc ctg tca	283
Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro Val His Thr Thr Leu Ser	
7 12 17 22	
aag tca gat gcc aaa aaa gcc gcc tca aag acg ctg ctg gag aag agt	331
Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys Thr Leu Leu Glu Lys Ser	
23 28 33 38	
cag ttt tca gat aag ccg gtg caa gac cgg ggt ttg gtg gtg acg gac	379
Gln Phe Ser Asp Lys Pro Val Gln Asp Arg Gly Leu Val Val Thr Asp	
39 44 49 54	
ctc aaa gct gag agt gtg gtt ctt gag cat cgc agc tac tgc tcg gca	427

Leu	Lys	Ala	Glu	Ser	Val	Val	Leu	Glu	His	Arg	Ser	Tyr	Cys	Ser	Ala	
55					60					65					70	
aag	gcc	cgg	gac	aga	cac	ttt	gct	ggg	gat	gta	ctg	ggc	tat	gtc	act	475
Lys	Ala	Arg	Asp	Arg	His	Phe	Ala	Gly	Asp	Val	Leu	Gly	Tyr	Val	Thr	
71					76					81					86	
cca	tgg	aac	agc	cat	ggc	tac	tat	gtc	acc	aag	gtc	ttt	ggg	agc	aag	523
Pro	Trp	Asn	Ser	His	Gly	Tyr	Tyr	Val	Thr	Lys	Val	Phe	Gly	Ser	Lys	
87					92					97					102	
ttc	aca	cag	atc	tca	ccc	gtc	tgg	ctg	cag	ctg	aag	aga	cgt	ggc	cgt	571
Phe	Thr	Gln	Ile	Ser	Pro	Val	Trp	Leu	Gln	Leu	Lys	Arg	Arg	Gly	Arg	
103					108					113					118	
gag	atg	ttt	gag	gtc	acg	ggc	ctc	cac	gac	gtg	gac	caa	ggg	tgg	atg	619
Glu	Met	Phe	Glu	Val	Thr	Gly	Leu	His	Asp	Val	Asp	Gln	Gly	Trp	Met	
119					124					129					134	
cga	gct	gtc	agg	aag	cat	gcc	aag	ggc	ctg	cac	ata	gtg	cct	cgg	ctc	667
Arg	Ala	Val	Arg	Lys	His	Ala	Lys	Gly	Leu	His	Ile	Val	Pro	Arg	Leu	
135					140					145					150	
ctg	ttt	gag	gac	tgg	act	tac	gat	gat	ttc	cgg	aac	gtc	tta	tac	agt	715
Leu	Phe	Glu	Asp	Trp	Thr	Tyr	Asp	Asp	Phe	Arg	Asn	Val	Leu	Tyr	Ser	
151					156					161					166	
gag	gat	gag	ata	gag	gag	ctg	agc	aag	acc	gtg	gtc	cag	gtg	gca	aag	763
Glu	Asp	Glu	Ile	Glu	Glu	Leu	Ser	Lys	Thr	Val	Val	Gln	Val	Ala	Lys	
167					172					177					182	
aac	cag	cat	ttc	gat	ggc	ttc	gtg	gtg	gag	gtc	tgg	aac	cag	ctg	cta	811
Asn	Gln	His	Phe	Asp	Gly	Phe	Val	Val	Glu	Val	Trp	Asn	Gln	Leu	Leu	
183					188					193					198	
agc	cag	aag	cgc	gtg	ggc	ctc	atc	cac	atg	ctc	acc	cac	ttg	gcc	gag	859
Ser	Gln	Lys	Arg	Val	Gly	Leu	Ile	His	Met	Leu	Thr	His	Leu	Ala	Glu	
199					204					209					214	
gct	ctg	cac	cag	gcc	cgg	ctg	ctg	gcc	ctc	ctg	gtc	atc	ccg	cct	gcc	907
Ala	Leu	His	Gln	Ala	Arg	Leu	Leu	Ala	Leu	Leu	Val	Ile	Pro	Pro	Ala	
215					220					225					230	
atc	acc	ccc	ggg	acc	gac	cag	ctg	ggc	atg	ttc	acg	cac	aag	gag	ttt	955
Ile	Thr	Pro	Gly	Thr	Asp	Gln	Leu	Gly	Met	Phe	Thr	His	Lys	Glu	Phe	
231					236					241					246	
gag	cag	ctg	gcc	ccc	gtg	ctg	gat	ggt	ttc	agc	ctc	atg	acc	tac	gac	1003
Glu	Gln	Leu	Ala	Pro	Val	Leu	Asp	Gly	Phe	Ser	Leu	Met	Thr	Tyr	Asp	
247					252					257					262	
tac	tct	aca	gcg	cat	cag	cct	ggc	cct	aat	gca	ccc	ctg	tcc	tgg	gtt	1051
Tyr	Ser	Thr	Ala	His	Gln	Pro	Gly	Pro	Asn	Ala	Pro	Leu	Ser	Trp	Val	
263					268					273					278	
cga	gcc	tgc	gtc	cag	gtc	ctg	gac	ccg	aag	tcc	aag	tgg	cga	agc	aaa	1099
Arg	Ala	Cys	Val	Gln	Val	Leu	Asp	Pro	Lys	Ser	Lys	Trp	Arg	Ser	Lys	

279	284	289	294	
atc ctc ctg ggg ctc aac ttc tat ggt atg gac tac gcg acc tcc aag				1147
Ile Leu Leu Gly Leu Asn Phe Tyr Gly Met Asp Tyr Ala Thr Ser Lys				
295	300	305	310	
gat gcc cgt gag cct gtt gtc ggg gcc agg tac atc cag aca ctg aag				1195
Asp Ala Arg Glu Pro Val Val Gly Ala Arg Tyr Ile Gln Thr Leu Lys				
311	316	321	326	
gac cac agg ccc cgg atg gtg tgg gac agc cag gcc tca gag cac ttc				1243
Asp His Arg Pro Arg Met Val Trp Asp Ser Gln Ala Ser Glu His Phe				
327	332	337	342	
ttc gag tac aag aag agc cgc agt ggg agg cac gtc gtc ttc tac cca				1291
Phe Glu Tyr Lys Lys Ser Arg Ser Gly Arg His Val Val Phe Tyr Pro				
343	348	353	358	
acc ctg aag tcc ctg cag gtg cgg ctg gag ctg gcc cgg gag ctg ggc				1339
Thr Leu Lys Ser Leu Gln Val Arg Leu Glu Leu Ala Arg Glu Leu Gly				
359	364	369	374	
gtt ggg gtc tct atc tgg gag ctg ggc cag ggc ctg gac tac ttc tac				1387
Val Gly Val Ser Ile Trp Glu Leu Gly Gln Gly Leu Asp Tyr Phe Tyr				
375	380	385	390	
gac ctg ctc tag gtg ggcattgcgg cctccgcggt ggacgtgttc ttttctaagc				1442
Asp Leu Leu *				
391				
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aaaa				1506

<210> 28  
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 <212> DNA  
 <213> Homo sapiens

<220>  
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gggcttcatg ccggatgtga tagtctgcag tcgtttcggt tggcagcctg gcgggtggga	180
gatgcggcgg ccacctgctg caaagaaccg aagggaaggt tagaagtacg aaggcagttt	240
ggagctgggg ctaagcagct gtcgcacggt cagatc atg ggc tcc acc aag cac	294
Met Gly Ser Thr Lys His	

tgg	ggc	gaa	tgg	ctc	ctg	aac	ttg	aag	gtg	gct	cca	gcc	ggc	gtc	ttt	342
Trp	Gly	Glu	Trp	Leu	Leu	Asn	Leu	Lys	Val	Ala	Pro	Ala	Gly	Val	Phe	
7					12					17					22	
ggt	gtg	gcc	ttt	cta	gcc	aga	gtc	gcc	ctg	gtt	ttc	tat	ggc	gtc	ttc	390
Gly	Val	Ala	Phe	Leu	Ala	Arg	Val	Ala	Leu	Val	Phe	Tyr	Gly	Val	Phe	
23					28					33					38	
cag	gac	cgg	acc	ctg	cac	gtg	agg	tat	acg	gac	atc	gac	tac	cag	gtc	438
Gln	Asp	Arg	Thr	Leu	His	Val	Arg	Tyr	Thr	Asp	Ile	Asp	Tyr	Gln	Val	
39					44					49					54	
ttc	acc	gac	gcc	gcg	cgc	ttc	gtc	acg	gag	ggg	cgc	tcg	cct	tac	ctg	486
Phe	Thr	Asp	Ala	Ala	Arg	Phe	Val	Thr	Glu	Gly	Arg	Ser	Pro	Tyr	Leu	
55					60					65					70	
aga	gcc	acg	tac	cgt	tac	acc	ccg	ctg	ctg	ggt	tgg	ctc	ctc	act	ccc	534
Arg	Ala	Thr	Tyr	Arg	Tyr	Thr	Pro	Leu	Leu	Gly	Trp	Leu	Leu	Thr	Pro	
71					76					81					86	
aac	atc	tac	ctc	agc	gag	ctc	ttt	gga	aag	ttt	ctc	ttc	atc	agc	tgc	582
Asn	Ile	Tyr	Leu	Ser	Glu	Leu	Phe	Gly	Lys	Phe	Leu	Phe	Ile	Ser	Cys	
87					92					97					102	
gac	ctc	ctc	acc	gct	ttc	ctc	tta	tac	cgc	ctg	ctg	ctg	ctg	aag	ggg	630
Asp	Leu	Leu	Thr	Ala	Phe	Leu	Leu	Tyr	Arg	Leu	Leu	Leu	Leu	Lys	Gly	
103					108					113					118	
ctg	ggg	cgc	cgc	cag	gct	tgt	ggc	tac	tgt	gtc	ttt	tgg	ctt	ctt	aac	678
Leu	Gly	Arg	Arg	Gln	Ala	Cys	Gly	Tyr	Cys	Val	Phe	Trp	Leu	Leu	Asn	
119					124					129					134	
ccc	ctg	cct	atg	gca	gta	tcc	agc	cgc	ggt	aat	gcg	gac	tct	att	gtc	726
Pro	Leu	Pro	Met	Ala	Val	Ser	Ser	Arg	Gly	Asn	Ala	Asp	Ser	Ile	Val	
135					140					145					150	
gcc	tcc	ctg	gtc	ctg	atg	gtc	ctc	tac	ttg	ata	aag	aaa	aga	ctc	gtc	774
Ala	Ser	Leu	Val	Leu	Met	Val	Leu	Tyr	Leu	Ile	Lys	Lys	Arg	Leu	Val	
151					156					161					166	
gcg	tgt	gca	gct	gta	ttc	tat	ggt	ttc	gcg	gtg	cat	atg	aag	ata	tat	822
Ala	Cys	Ala	Ala	Val	Phe	Tyr	Gly	Phe	Ala	Val	His	Met	Lys	Ile	Tyr	
167					172					177					182	
cca	gag	act	tac	atc	ctt	ccc	ata	acc	ctc	cac	ctg	ctt	cca	gat	cgc	870
Pro	Glu	Thr	Tyr	Ile	Leu	Pro	Ile	Thr	Leu	His	Leu	Leu	Pro	Asp	Arg	
183					188					193					198	
gac	aat	gac	aaa	agc	ctc	cgt	caa	ttc	cgg	aca	agg	ctg	tgt	aat	cgg	918
Asp	Asn	Asp	Lys	Ser	Leu	Arg	Gln	Phe	Arg	Thr	Arg	Leu	Cys	Asn	Arg	
199					204					209					214	
act	gcg	ctg	atg	ttt	gta	gca	gtt	gct	gga	ctc	acg	ttt	ttt	gcc	ctg	966
Thr	Ala	Leu	Met	Phe	Val	Ala	Val	Ala	Gly	Leu	Thr	Phe	Phe	Ala	Leu	
215					220					225					230	

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Ser Phe Gly Phe Tyr Tyr Glu Tyr Gly Trp Glu Phe Leu Glu His Thr	
231 236 241 246	
tac ttt tat cac ctg act agg cgg gat atc cgt cac aac ttt tct ccg	1062
Tyr Phe Tyr His Leu Thr Arg Arg Asp Ile Arg His Asn Phe Ser Pro	
247 252 257 262	
tac ttc tac atg ctg tat ttg act gca gag agc aag tgg agt ttt tcc	1110
Tyr Phe Tyr Met Leu Tyr Leu Thr Ala Glu Ser Lys Trp Ser Phe Ser	
263 268 273 278	
ctg gga att gct gca ttc ctg cca cag ctc atc ttg ctt tca gct gtg	1158
Leu Gly Ile Ala Ala Phe Leu Pro Gln Leu Ile Leu Leu Ser Ala Val	
279 284 289 294	
tct ttc gcc tat tac aga gac ctc gtt ttt tgt tgt ttt ctt cat acg	1206
Ser Phe Ala Tyr Tyr Arg Asp Leu Val Phe Cys Cys Phe Leu His Thr	
295 300 305 310	
tcc att ttt gtg act ttt aac aaa gtc tgc acc tcc cag tac ttt ctt	1254
Ser Ile Phe Val Thr Phe Asn Lys Val Cys Thr Ser Gln Tyr Phe Leu	
311 316 321 326	
tgg tac ctc tgc tta ctg cct ctt gtg atg cca cta gtc aga atg cct	1302
Trp Tyr Leu Cys Leu Leu Pro Leu Val Met Pro Leu Val Arg Met Pro	
327 332 337 342	
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Trp Lys Arg Ala Val Val Leu Leu Met Leu Trp Phe Ile Gly Gln Ala	
343 348 353 358	
atg tgg ctg gct cct gcc tat gtt cta gag ttt caa gga aag aac acc	1398
Met Trp Leu Ala Pro Ala Tyr Val Leu Glu Phe Gln Gly Lys Asn Thr	
359 364 369 374	
ttt ctg ttt att tgg tta gct ggt ttg ttc ttt ctt ctt atc aat tgt	1446
Phe Leu Phe Ile Trp Leu Ala Gly Leu Phe Phe Leu Leu Ile Asn Cys	
375 380 385 390	
tcc atc ctg att caa att att tcc cat tac aaa gaa gaa ccc ctg aca	1494
Ser Ile Leu Ile Gln Ile Ile Ser His Tyr Lys Glu Glu Pro Leu Thr	
391 396 401 406	
gag aga atc aaa tat gac tag tg tatgttccac accctctgct actgtgttac	1547
Glu Arg Ile Lys Tyr Asp *	
407 412	
attctgattg tcttgtatgg accagaagag agctttggga cattttttct gaacattcta	1607
agcattctag tgaaagttcc catgttccaa cagaacttaa aagcaatggt tgccttatat	1667
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                   Met Arg Gly Ala Ala Ser Ala Ser Val Arg Glu Pro Thr  
                   1                  5                  10  
 ccg ctc ccg ggt aga ggc gcc ccc cgc aca aag ccc cgg gcg ggc cga 158  
 Pro Leu Pro Gly Arg Gly Ala Pro Arg Thr Lys Pro Arg Ala Gly Arg  
   14                  19                  24                  29  
 ggc ccg act gta ggg act cca gcc acc ttg gcc ctc cct gcc cgg gga 206  
 Gly Pro Thr Val Gly Thr Pro Ala Thr Leu Ala Leu Pro Ala Arg Gly  
   30                  35                  40                  45  
 agg ccg cgc tca agg aat ggc ctc gca tcc aaa ggc cag cga gga gcg 254  
 Arg Pro Arg Ser Arg Asn Gly Leu Ala Ser Lys Gly Gln Arg Gly Ala  
   46                  51                  56                  61  
 gcc cct acg ggg cct ggg cac aga gct ctg cct tcc agg gac act gct 302  
 Ala Pro Thr Gly Pro Gly His Arg Ala Leu Pro Ser Arg Asp Thr Ala  
   62                  67                  72                  77  
 ctt ccc cag gag aga aac aag aag ctg gag gct gtg ggg aca gga att 350  
 Leu Pro Gln Glu Arg Asn Lys Lys Leu Glu Ala Val Gly Thr Gly Ile  
   78                  83                  88                  93  
 gaa cct aaa gcc atg tcc cag ggc ttg gtg aca ttt ggg gat gtg gct 398  
 Glu Pro Lys Ala Met Ser Gln Gly Leu Val Thr Phe Gly Asp Val Ala  
   94                  99                  104                  109  
 gta gat ttc tcc caa gag gag tgg gag tgg ctg aac ccc att cag agg 446  
 Val Asp Phe Ser Gln Glu Glu Trp Glu Trp Leu Asn Pro Ile Gln Arg  
  110                  115                  120                  125  
 aac ttg tac agg aag gtg atg ttg gag aac tac agg aac ctg gca tcg 494  
 Asn Leu Tyr Arg Lys Val Met Leu Glu Asn Tyr Arg Asn Leu Ala Ser  
  126                  131                  136                  141  
 ctg gga ctt tgt gtt tct aag ccc gat gtg atc tcc tcg ttg gaa caa 542  
 Leu Gly Leu Cys Val Ser Lys Pro Asp Val Ile Ser Ser Leu Glu Gln  
  142                  147                  152                  157  
 gga aaa gag cct tgg aca gtg aag cga aag atg aca aga gcc tgg tgc 590  
 Gly Lys Glu Pro Trp Thr Val Lys Arg Lys Met Thr Arg Ala Trp Cys

158		163		168		173	
cca gac ttg aag gct	gtg tgg aag atc aag	gag tta cct ctc aag aag	638				
Pro Asp Leu Lys Ala	Val Trp Lys Ile Lys	Glu Leu Pro Leu Lys Lys					
174	179	184	189				
gac ttc tgc gaa gga	aag cta tcc cag gca	gtg ata aca gag aga ctc	686				
Asp Phe Cys Glu Gly	Lys Leu Ser Gln Ala	Val Ile Thr Glu Arg Leu					
190	195	200	205				
aca agc tat aat ctg	gag tac tct ctg tta	ggg gaa cac tgg gat tat	734				
Thr Ser Tyr Asn Leu	Glu Tyr Ser Leu Leu	Gly Glu His Trp Asp Tyr					
206	211	216	221				
gat gct ctg ttt gag	aca cag ccg ggc ttg	gtg act atc aaa aac ctg	782				
Asp Ala Leu Phe Glu	Thr Gln Pro Gly Leu	Val Thr Ile Lys Asn Leu					
222	227	232	237				
gct gtt gac ttc cgc	cag cag cta cac cca	gct cag aag aat ttc tgt	830				
Ala Val Asp Phe Arg	Gln Gln Leu His Pro	Ala Gln Lys Asn Phe Cys					
238	243	248	253				
aag aat ggg ata tgg	gag aac aac agt gac	ctg gga tca gca gga cat	878				
Lys Asn Gly Ile Trp	Glu Asn Asn Ser Asp	Leu Gly Ser Ala Gly His					
254	259	264	269				
tgt gtg gct aag cca	gat tta gtc tct tta	cta gag caa gag aag gag	926				
Cys Val Ala Lys Pro	Asp Leu Val Ser Leu	Leu Glu Gln Glu Lys Glu					
270	275	280	285				
ccc tgg atg gtg aag	cga gag ctg aca gga	agc ctg ttc tca ggc cag	974				
Pro Trp Met Val Lys	Arg Glu Leu Thr Gly	Ser Leu Phe Ser Gly Gln					
286	291	296	301				
cga tct gta cat gag	acc cag gaa tta ttt	cca aag caa gat tca tat	1022				
Arg Ser Val His Glu	Thr Gln Glu Leu Phe	Pro Lys Gln Asp Ser Tyr					
302	307	312	317				
gct gaa ggg gta aca	gac aga acc tca aac	act aaa ctt gat tgt tcc	1070				
Ala Glu Gly Val Thr	Asp Arg Thr Ser Asn	Thr Lys Leu Asp Cys Ser					
318	323	328	333				
agt ttc aga gaa aat	tgg gat tct gac tat	gtg ttc gga agg aag ctt	1118				
Ser Phe Arg Glu Asn	Trp Asp Ser Asp Tyr	Val Phe Gly Arg Lys Leu					
334	339	344	349				
gca gta ggt caa gag	aca caa ttc agg caa	gag cca att act cat aac	1166				
Ala Val Gly Gln Glu	Thr Gln Phe Arg Gln	Glu Pro Ile Thr His Asn					
350	355	360	365				
aaa acc ctc tct aag	gaa aga gaa cgt aca	tat aac aaa tct gga aga	1214				
Lys Thr Leu Ser Lys	Glu Arg Glu Arg Thr	Tyr Asn Lys Ser Gly Arg					
366	371	376	381				
tgg tcc tat ttg gac	gat tca gaa gag aaa	gtt cat aat cgt gat tca	1262				
Trp Ser Tyr Leu Asp	Asp Ser Glu Glu Lys	Val His Asn Arg Asp Ser					
382	387	392	397				





Pro Ser Thr Ser Asn Pro Val Asp Leu Phe Pro Lys Phe Leu Trp Asn  
846 851 856 861

cca tcc tcc ctc cca tca cca tag cctcgagacg tcatttctgt ttgactactc 2708  
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862 867

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aaattgggta atgtgtgaga tgtgctcagc acagtgcctg gtccatagta agtgctcagt 2888  
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ctttaaaaag atg cag cac ctg gac tgc gac ctt tgg ctc cag ctg gaa 169  
Met Gln His Leu Asp Cys Asp Leu Trp Leu Gln Leu Glu  
1 5 10

ctt tcc agc cag tgt gtg ctt ctg ggg aac gga gtg gct atg aat ctg 217  
Leu Ser Ser Gln Cys Val Leu Leu Gly Asn Gly Val Ala Met Asn Leu  
14 19 24 29

cat gta aag act ttg tcc ctc atg act tgg agg tcc aga ttc ctg gaa 265  
His Val Lys Thr Leu Ser Leu Met Thr Trp Arg Ser Arg Phe Leu Glu  
30 35 40 45

gag tct ttt tgg tca ctg gag gaa aca gcg gca ttg gca aag caa ctg 313  
Glu Ser Phe Trp Ser Leu Glu Glu Thr Ala Ala Leu Ala Lys Gln Leu  
46 51 56 61

ccc ttg aaa tcg cca agc gag aac att ttt ctg cac att gtg gac ttg 361  
Pro Leu Lys Ser Pro Ser Glu Asn Ile Phe Leu His Ile Val Asp Leu  
62 67 72 77

tct gat ccc aag caa atc tgg aaa ttt gtt gaa aat ttc aag cag gaa 409  
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tgctgcag atg ctg gag atg aac atg gcc atc gcc ttc ccc gca gcg ccc 170  
Met Leu Glu Met Asn Met Ala Ile Ala Phe Pro Ala Ala Pro  
1 5 10

ctg ctg acc gtc atc ctg gcc ctc gtc ggg atg gag gcc atc atg tcg 218  
Leu Leu Thr Val Ile Leu Ala Leu Val Gly Met Glu Ala Ile Met Ser  
15 20 25 30

gag ttc ttc aac gac acc acc acc gcc ttc tac atc atc ctc atc gtg 266  
Glu Phe Phe Asn Asp Thr Thr Thr Ala Phe Tyr Ile Ile Leu Ile Val  
31 36 41 46

tgg ctc gcg gac cag tat gac gcc atc tgc tgc cac acc agc acc agc 314  
Trp Leu Ala Asp Gln Tyr Asp Ala Ile Cys Cys His Thr Ser Thr Ser  
47 52 57 62

aag cgg cat tgg ctg cgg ttc ttc tat ctc tac cac ttc gcc ttc tat 362  
Lys Arg His Trp Leu Arg Phe Phe Tyr Leu Tyr His Phe Ala Phe Tyr  
63 68 73 78

gcc tat cac tac cgc ttc aat ggg cag tat agc agc ctg gcc ctg gtc 410  
Ala Tyr His Tyr Arg Phe Asn Gly Gln Tyr Ser Ser Leu Ala Leu Val  
79 84 89 94

acc tcc tgg ctc ttc atc cag cat tcc atg atc tac ttc ttc cac cac 458  
Thr Ser Trp Leu Phe Ile Gln His Ser Met Ile Tyr Phe Phe His His  
95 100 105 110

tac gag ctg cct gcc atc ctg cag cag gtc cgc atc cag gag atg ctg 506  
Tyr Glu Leu Pro Ala Ile Leu Gln Gln Val Arg Ile Gln Glu Met Leu  
111 116 121 126

ctt cag gcg ccg aca ctg ggc ccc ggg acc ccc acg gcg ctg ccc gat 554  
Leu Gln Ala Pro Thr Leu Gly Pro Gly Thr Pro Thr Ala Leu Pro Asp  
127 132 137 142

gac atg aac aac aac tcg ggc gcc ccg gct aca gcc cct gac tct gcc 602  
Asp Met Asn Asn Asn Ser Gly Ala Pro Ala Thr Ala Pro Asp Ser Ala  
143 148 153 158

ggc cag ccc ccc gcc ctg ggc ccc gtc tcg cct ggg ggc cag cgg gag 650  
Gly Gln Pro Pro Ala Leu Gly Pro Val Ser Pro Gly Gly Gln Arg Glu  
159 164 169 174

tcc cgg gcc tgt ggc agc ggc gcc cag ctc cct ggt ggc cgc ggc agc 698  
Ser Arg Ala Cys Gly Ser Gly Ala Gln Leu Pro Gly Gly Arg Gly Ser







Leu	His	Leu	Ile	His	Ile	Thr	Val	Asn	Thr	Leu	Asn	Ala	Gln	Tyr	His	
191					196					201					206	
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Ser	Cys	Lys	Pro	His	Ala	Thr	Ala	Gly	Pro	Leu	Tyr	Ser	Asp	Asn	Ser	
207					212					217					222	
aac	ata	agc	aga	tac	agc	gaa	aaa	gaa	aaa	gaa	gaa	gat	agt	gtt	ttt	1141
Asn	Ile	Ser	Arg	Tyr	Ser	Glu	Lys	Glu	Lys	Glu	Glu	Asp	Ser	Val	Phe	
223					228					233					238	
gat	gaa	tct	gat	att	cat	gat	aca	cct	act	gga	ccc	tgc	aat	aaa	gag	1189
Asp	Glu	Ser	Asp	Ile	His	Asp	Thr	Pro	Thr	Gly	Pro	Cys	Asn	Lys	Glu	
239					244					249					254	
tct	caa	act	ttt	ttt	gca	aga	ttg	aaa	aga	ata	ggc	ggc	agc	aaa	atg	1237
Ser	Gln	Thr	Phe	Phe	Ala	Arg	Leu	Lys	Arg	Ile	Gly	Gly	Ser	Lys	Met	
255					260					265					270	
gtg	aaa	tat	cag	ccg	gtt	gag	atg	aat	gtt	cag	aga	agt	gaa	ata	gaa	1285
Val	Lys	Tyr	Gln	Pro	Val	Glu	Met	Asn	Val	Gln	Arg	Ser	Glu	Ile	Glu	
271					276					281					286	
ctg	gct	gaa	tat	aga	gag	acg	ggg	gca	tta	caa	gac	agc	ctt	ctc	cac	1333
Leu	Ala	Glu	Tyr	Arg	Glu	Thr	Gly	Ala	Leu	Gln	Asp	Ser	Leu	Leu	His	
287					292					297					302	
tgt	gtg	aga	gaa	gaa	agc	att	ccg	aaa	aaa	aag	cta	cgc	tct	ttc	aaa	1381
Cys	Val	Arg	Glu	Glu	Ser	Ile	Pro	Lys	Lys	Lys	Leu	Arg	Ser	Phe	Lys	
303					308					313					318	
caa	aaa	tct	ctt	gat	ata	ggg	aat	gca	gac	tcg	ctt	ttg	ttt	aca	tta	1429
Gln	Lys	Ser	Leu	Asp	Ile	Gly	Asn	Ala	Asp	Ser	Leu	Leu	Phe	Thr	Leu	
319					324					329					334	
gac	gaa	cat	cgt	agg	aag	tcg	tgc	ata	gat	cgg	tgt	gac	ata	gag	aag	1477
Asp	Glu	His	Arg	Arg	Lys	Ser	Cys	Ile	Asp	Arg	Cys	Asp	Ile	Glu	Lys	
335					340					345					350	
cct	ccg	acc	caa	gct	gcg	tat	atc	gca	caa	aga	cca	aac	gac	cct	gga	1525
Pro	Pro	Thr	Gln	Ala	Ala	Tyr	Ile	Ala	Gln	Arg	Pro	Asn	Asp	Pro	Gly	
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cgt	tct	aga	cag	aac	tct	gct	acg	agg	cct	gac	aat	agt	gaa	atc	ccc	1573
Arg	Ser	Arg	Gln	Asn	Ser	Ala	Thr	Arg	Pro	Asp	Asn	Ser	Glu	Ile	Pro	
367					372					377					382	
gag	aac	cca	gct	atg	gaa	ggg	ttt	cca	gat	gct	cga	agg	cct	gtc	ata	1621
Glu	Asn	Pro	Ala	Met	Glu	Gly	Phe	Pro	Asp	Ala	Arg	Arg	Pro	Val	Ile	
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Pro	Glu	Val	Arg	Leu	Asn	Cys	Met	Glu	Thr	Phe	Glu	Val	Lys	Val	Asp	
399					404					409					414	
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Ser	Pro	Val	Lys	Pro	Ala	Pro	Lys	Glu	Asp	Leu	Asp	Leu	Ile	Asp	Leu	





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Thr	Thr	Phe	Ser	Asn	Gln	Ala	Glu	Ser	Met	Met	Val	Pro	Gly	Asn	Ala	
879					884					889					894	
gcg	ggg	gtg	gcc	aag	cag	ttc	ctg	cgc	tgc	atc	ttc	cat	cag	ttg	gcc	3157
Ala	Gly	Val	Ala	Lys	Gln	Phe	Leu	Arg	Cys	Ile	Phe	His	Gln	Leu	Ala	
895					900					905					910	
ccc	aac	ggc	atc	ttc	ccg	cag	ctg	ttc	caa	agc	acg	atc	aaa	gat	ggg	3205
Pro	Asn	Gly	Ile	Phe	Pro	Gln	Leu	Phe	Gln	Ser	Thr	Ile	Lys	Asp	Gly	
911					916					921					926	
act	ttt	tta	cgg	acc	tta	gcc	tcg	tct	ctg	atg	gac	ttc	aat	gag	ctg	3253
Thr	Phe	Leu	Arg	Thr	Leu	Ala	Ser	Ser	Leu	Met	Asp	Phe	Asn	Glu	Leu	
927					932					937					942	
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Ser	Ser	Ile	Ala	Ala	Leu	Ser	Gln	Leu	Leu	Glu	Gly	Leu	Asn	Asn	Lys	
943					948					953					958	
aag	aat	tta	cca	gca	ggg	ggc	gct	atg	att	cgc	tgt	ttg	gaa	aac	att	3349
Lys	Asn	Leu	Pro	Ala	Gly	Gly	Ala	Met	Ile	Arg	Cys	Leu	Glu	Asn	Ile	
959					964					969					974	
gca	acc	ttc	atg	gaa	gct	ttg	cct	atg	gat	tct	cct	agt	agc	ctc	tgg	3397
Ala	Thr	Phe	Met	Glu	Ala	Leu	Pro	Met	Asp	Ser	Pro	Ser	Ser	Leu	Trp	
975					980					985					990	
acc	aca	att	agc	aac	cag	ttt	cag	aca	ttt	ttt	gcc	aag	ctg	cct	tgt	3445
Thr	Thr	Ile	Ser	Asn	Gln	Phe	Gln	Thr	Phe	Phe	Ala	Lys	Leu	Pro	Cys	
991					996					1001					1006	
gtt	tta	cct	ctg	aag	tgt	tct	tta	gat	tcc	agt	tta	aga	att	atg	att	3493
Val	Leu	Pro	Leu	Lys	Cys	Ser	Leu	Asp	Ser	Ser	Leu	Arg	Ile	Met	Ile	
1007					1012					1017					1022	
tgc	ctc	ttg	aag	atc	cct	tct	acc	aat	gct	aca	agg	agt	ttg	ttg	gaa	3541
Cys	Leu	Leu	Lys	Ile	Pro	Ser	Thr	Asn	Ala	Thr	Arg	Ser	Leu	Leu	Glu	
1023					1028					1033					1038	
cca	ttt	tca	aaa	ctg	ctc	agc	ttt	gta	att	cag	aat	gcc	gtc	ttc	act	3589
Pro	Phe	Ser	Lys	Leu	Leu	Ser	Phe	Val	Ile	Gln	Asn	Ala	Val	Phe	Thr	
1039					1044					1049					1054	
ctg	gcc	tac	ctg	gtg	gag	ctg	tgt	ggc	tta	tgt	tac	cga	gct	ttc	act	3637
Leu	Ala	Tyr	Leu	Val	Glu	Leu	Cys	Gly	Leu	Cys	Tyr	Arg	Ala	Phe	Thr	
1055					1060					1065					1070	
aag	gaa	cga	gat	aaa	ttc	tac	ttg	tct	cgt	agt	gtt	gtt	cta	gaa	ctt	3685
Lys	Glu	Arg	Asp	Lys	Phe	Tyr	Leu	Ser	Arg	Ser	Val	Val	Leu	Glu	Leu	
1071					1076					1081					1086	

Leu	Leu	Val	Gln	Phe	Ile	Cys	Ala	Asp	Ala	Gly	Thr	Lys	Leu	Ala	Glu	
1103					1108					1113					1118	
tca	aca	atc	ctg	agc	aag	cag	atg	ata	gcc	tct	gta	cct	gga	tgt	ggg	3829
Ser	Thr	Ile	Leu	Ser	Lys	Gln	Met	Ile	Ala	Ser	Val	Pro	Gly	Cys	Gly	
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act	gca	gcg	atg	gag	tgt	gtg	agg	cag	tac	atc	aac	gaa	gtg	ctg	gat	3877
Thr	Ala	Ala	Met	Glu	Cys	Val	Arg	Gln	Tyr	Ile	Asn	Glu	Val	Leu	Asp	
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ttc	atg	gca	gac	atg	cac	acg	ctg	acc	aaa	ctg	aag	agc	cac	atg	aag	3925
Phe	Met	Ala	Asp	Met	His	Thr	Leu	Thr	Lys	Leu	Lys	Ser	His	Met	Lys	
1151					1156					1161					1166	
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Thr	Cys	Ser	Gln	Pro	Leu	His	Glu	Asp	Thr	Phe	Gly	Gly	His	Leu	Lys	
1167					1172					1177					1182	
gtg	ggg	ctg	gcc	cag	att	gca	gcc	atg	gac	atc	tca	cgg	ggc	aac	cac	4021
Val	Gly	Leu	Ala	Gln	Ile	Ala	Ala	Met	Asp	Ile	Ser	Arg	Gly	Asn	His	
1183					1188					1193					1198	
aga	gat	aac	aaa	gct	gtg	atc	cgc	tat	ctg	cct	tgg	ctt	tat	cat	ccc	4069
Arg	Asp	Asn	Lys	Ala	Val	Ile	Arg	Tyr	Leu	Pro	Trp	Leu	Tyr	His	Pro	
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ccc	tct	gca	atg	cag	caa	gga	cct	aaa	gaa	ttc	att	gag	tgt	gtc	tcc	4117
Pro	Ser	Ala	Met	Gln	Gln	Gly	Pro	Lys	Glu	Phe	Ile	Glu	Cys	Val	Ser	
1215					1220					1225					1230	
cat	atc	cga	ctg	ttg	tcc	tgg	ctg	ctg	ctg	ggt	tcc	ctc	act	cac	aat	4165
His	Ile	Arg	Leu	Leu	Ser	Trp	Leu	Leu	Leu	Gly	Ser	Leu	Thr	His	Asn	
1231					1236					1241					1246	
gca	gtg	tgc	cca	aat	gcc	tcc	tct	ccc	tgc	ctg	ccc	att	cct	ctg	gat	4213
Ala	Val	Cys	Pro	Asn	Ala	Ser	Ser	Pro	Cys	Leu	Pro	Ile	Pro	Leu	Asp	
1247					1252					1257					1262	
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Ala	Gly	Ser	His	Val	Ala	Asp	His	Leu	Ile	Val	Ile	Leu	Ile	Gly	Phe	
1263					1268					1273					1278	
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Pro	Glu	Gln	Ser	Lys	Thr	Ser	Val	Leu	His	Met	Cys	Ser	Leu	Phe	His	
1279					1284					1289					1294	
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Ala	Phe	Ile	Phe	Ala	Gln	Leu	Trp	Thr	Val	Tyr	Cys	Glu	Gln	Ser	Ala	
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gtc	gct	aca	aat	ctc	caa	aat	cag	aat	gaa	ttc	agc	ttc	acg	gcg	ata	4405
Val	Ala	Thr	Asn	Leu	Gln	Asn	Gln	Asn	Glu	Phe	Ser	Phe	Thr	Ala	Ile	
1311					1316					1321					1326	
ctg	aca	gca	cta	gaa	ttt	tgg	agt	agg	gtg	aca	ccc	agc	atc	ctt	cag	4453
Leu	Thr	Ala	Leu	Glu	Phe	Trp	Ser	Arg	Val	Thr	Pro	Ser	Ile	Leu	Gln	

1327	1332	1337	1342	
cta atg gcc cat aac aaa gtg atg gta gaa atg gtg tgt ctc cat gtg				4501
Leu Met Ala His Asn Lys Val Met Val Glu Met Val Cys Leu His Val				
1343	1348	1353	1358	
att agt tta atg gag gca ttg cag gaa tgc aat tcg acc att ttt gtc				4549
Ile Ser Leu Met Glu Ala Leu Gln Glu Cys Asn Ser Thr Ile Phe Val				
1359	1364	1369	1374	
aag ctg ata cct atg tgg ttg cca atg att cag tca aat atc aag cac				4597
Lys Leu Ile Pro Met Trp Leu Pro Met Ile Gln Ser Asn Ile Lys His				
1375	1380	1385	1390	
tta tct gcg gga ctc cag ctt cgc ctc cag gct att cag aac cac gtg				4645
Leu Ser Ala Gly Leu Gln Leu Arg Leu Gln Ala Ile Gln Asn His Val				
1391	1396	1401	1406	
aac cac cac agc cta agg acg ctg ccg ggc tcg ggc cag agc agt gct				4693
Asn His His Ser Leu Arg Thr Leu Pro Gly Ser Gly Gln Ser Ser Ala				
1407	1412	1417	1422	
ggc ctg gca gcc ctc cga aag tgg ttg cag tgc act cag ttc aaa atg				4741
Gly Leu Ala Ala Leu Arg Lys Trp Leu Gln Cys Thr Gln Phe Lys Met				
1423	1428	1433	1438	
gcc cag gtg gag atc cag tcc tcg gaa gca gcc tct caa ttt tat cct				4789
Ala Gln Val Glu Ile Gln Ser Ser Glu Ala Ala Ser Gln Phe Tyr Pro				
1439	1444	1449	1454	
cta tga gtggactcct cggcgctcag tgtcaacact ctggtttagc aataatgggt				4845
Leu *				
1455				
ttaaaaacaa acaatttgat ccaagcaggt tggggaacat attggtactg tacattctct				4905
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tgccctcgctt	cccggcgcg	tcgcagccct	cagcccactt	aggata	atg gcg aca	175
					Met Ala Thr	
					1	
gct gag gta	ctg aac att	ggt aaa aaa	tta tat	gag ggt	aaa aca aaa	223
Ala Glu Val	Leu Asn Ile	Gly Lys Lys	Leu Tyr	Glu Gly Lys	Thr Lys	
4	9		14		19	
gaa gtc tac	gaa ttg tta	gac agt cca	gga aaa	gtc ctc	ctg cag tcc	271
Glu Val Tyr	Glu Leu Leu	Asp Ser Pro	Gly Lys	Val Leu Leu	Gln Ser	
20	25		30		35	
aag gac cag	att aca gca	gga aat gca	gct aga	aaa aac	cac ctg gaa	319
Lys Asp Gln	Ile Thr Ala	Gly Asn Ala	Ala Arg	Lys Asn His	Leu Glu	
36	41		46		51	
gga aaa gct	gca atc tca	aat aaa atc	acc agt	tgt att	ttt cag tta	367
Gly Lys Ala	Ala Ile Ser	Asn Lys Ile	Thr Ser	Cys Ile Phe	Gln Leu	
52	57		62		67	
tta cag gaa	gca ggt att	aaa act gcc	ttc acc	aga aaa	tgt ggg gag	415
Leu Gln Glu	Ala Gly Ile	Lys Thr Ala	Phe Thr	Arg Lys Cys	Gly Glu	
68	73		78		83	
aca gct ttc	att gca ccg	cag tgt gaa	atg att	cca att	gaa tgg gtt	463
Thr Ala Phe	Ile Ala Pro	Gln Cys Glu	Met Ile	Pro Ile Glu	Trp Val	
84	89		94		99	
tgc aga aga	ata gca act	ggt tct ttt	ctc aaa	aga aat	cct ggt gtc	511
Cys Arg Arg	Ile Ala Thr	Gly Ser Phe	Leu Lys	Arg Asn Pro	Gly Val	
100	105		110		115	
aag gaa gga	tat aag ttt	tac cca cct	aaa gtg	gag ttg	ttt ttc aag	559
Lys Glu Gly	Tyr Lys Phe	Tyr Pro Pro	Lys Val	Glu Leu Phe	Phe Lys	
116	121		126		131	
gat gat gcc	aat aat gac	cca cag tgg	tct gag	gaa cag	ctg att gct	607
Asp Asp Ala	Asn Asn Asp	Pro Gln Trp	Ser Glu	Glu Glu Gln	Leu Ile Ala	
132	137		142		147	
gca aaa ttt	tgc ttt gct	gga ctt ctt	ata ggc	cag act	gaa gtg gat	655
Ala Lys Phe	Cys Phe Ala	Gly Leu Leu	Ile Gly	Gln Thr Glu	Val Asp	
148	153		158		163	
atc atg agt	cat gct aca	cag gct ata	ttt gaa	ata ctg	gag aaa tcc	703
Ile Met Ser	His Ala Thr	Gln Ala Ile	Phe Glu	Ile Leu Glu	Lys Ser	
164	169		174		179	
tgg ttg ccc	cag aat tgt	aca ctg gtt	gat atg	aag att	gaa ttt ggt	751
Trp Leu Pro	Gln Asn Cys	Thr Leu Val	Asp Met	Lys Ile Glu	Phe Gly	
180	185		190		195	
gtt gat gta	acc acc aaa	gaa att gtt	ctt gct	gat gtt	att gac aat	799
Val Asp Val	Thr Thr Lys	Glu Ile Val	Leu Ala	Asp Val Ile	Asp Asn	
196	201		206		211	





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tagagaacac aaataaaatg tattagtga ca 1568

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caaatgggga ggggactggc tcagcatccg gagccaaaac aggaatagaa ctggaagctg 180  
agcctggagc gggttctgggc ttttggttct ctgcatcaac acagccagc atg cct 235  
Met Pro  
1  
atg att tct gtg ctg ggc aaa atg ttt ctg tgg cag cgt gaa ggg cct 283  
Met Ile Ser Val Leu Gly Lys Met Phe Leu Trp Gln Arg Glu Gly Pro  
3 8 13 18  
gga gga cga tgg act tgt cag aca agt cgc aga gtg tcc tcg gac ccc 331  
Gly Gly Arg Trp Thr Cys Gln Thr Ser Arg Arg Val Ser Ser Asp Pro  
19 24 29 34  
gct tgg gct gtg gag tgg atc gaa ctt cct cgg ggt ctc tct cta tcc 379  
Ala Trp Ala Val Glu Trp Ile Glu Leu Pro Arg Gly Leu Ser Leu Ser  
35 40 45 50  
tct ttg gga tct gct cga acc ctc cga ggc tgg agc agg tcc tcc cgc 427  
Ser Leu Gly Ser Ala Arg Thr Leu Arg Gly Trp Ser Arg Ser Ser Arg  
51 56 61 66  
cct tcc tcg gtg gac agt cag gac ttg cca gag gtg aat gtt gga gac 475  
Pro Ser Ser Val Asp Ser Gln Asp Leu Pro Glu Val Asn Val Gly Asp  
67 72 77 82  
aca gtc gcg atg ctg ccc aag tcc cgg cga gcc cta act atc cag gag 523  
Thr Val Ala Met Leu Pro Lys Ser Arg Arg Ala Leu Thr Ile Gln Glu  
83 88 93 98  
atc gct gcg ctg gcc agg tcc tcc ctg cat ggt att tcc cag gtg gtg 571  
Ile Ala Ala Leu Ala Arg Ser Ser Leu His Gly Ile Ser Gln Val Val  
99 104 109 114  
aag gac cac gtg acc aag cct acc gcc atg gcc cag ggc cga gtg gct 619  
Lys Asp His Val Thr Lys Pro Thr Ala Met Ala Gln Gly Arg Val Ala



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tcc tta gat gag gat gag gca gag cca gag gaa cag tga cccacatcat      1340
Ser Leu Asp Glu Asp Glu Ala Glu Pro Glu Glu Gln  *
355                      360                      365

gcctggcagt ggcatgcatc ccccggtgc tgccaggggc agagccttct gtgcccagt      1400
gtgggctcaa ggctcccagc agagctccac agcctagagg gctcctggga gcgctcgctt      1460
ctccgttggtg tgttttgcat gaaagtgttt ggagaggagg caggggctgg gctgggggag      1520
catgtcctgc cccactccc ggggcttgcc ggggggttgcc cgggggcctc tggggcatgg      1580
ctacagctgt ggcagacagt gatgttcattg ttcttaaaat gccacacaca catttcctcc      1640
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<213> Homo sapiens

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<220>
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<222> (72)..(1958)

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          Met Ser Pro Gly Gly Lys Phe Asp Phe Asp Asp Gly Gly
              1              5              10

tgc tac gtg ggg ggc tgg gag gcg ggg cgg gca cat ggc tac ggc gtg      158
Cys Tyr Val Gly Gly Trp Glu Ala Gly Arg Ala His Gly Tyr Gly Val
 14              19              24              29

tgc acg ggc ccc ggc gcc cag ggc gag tac agc ggc tgc tgg gca cac      206
Cys Thr Gly Pro Gly Ala Gln Gly Glu Tyr Ser Gly Cys Trp Ala His
 30              35              40              45

ggc ttc gag tca ctg ggc gtc ttc acg ggg ccc ggc gga cac agc tac      254
Gly Phe Glu Ser Leu Gly Val Phe Thr Gly Pro Gly Gly His Ser Tyr
 46              51              56              61

cag ggc cac tgg cag cag ggc aag cgc gaa ggg ctg ggc gtg gag cgc      302
Gln Gly His Trp Gln Gln Gly Lys Arg Glu Gly Leu Gly Val Glu Arg
 62              67              72              77

aag agc cgc tgg acg tac cgc ggc gag tgg ctg ggc ggg ctg aag ggg      350
Lys Ser Arg Trp Thr Tyr Arg Gly Glu Trp Leu Gly Gly Leu Lys Gly
 78              83              88              93

cgc agc ggc gtg tgg gaa agc gtg tcc ggc ctg cgc tac gcc ggg ctc      398

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Arg	Ser	Gly	Val	Trp	Glu	Ser	Val	Ser	Gly	Leu	Arg	Tyr	Ala	Gly	Leu	
94					99					104					109	
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Trp	Lys	Asp	Gly	Phe	Gln	Asp	Gly	Tyr	Gly	Thr	Glu	Thr	Tyr	Ser	Asp	
110					115					120					125	
gga	ggc	acc	tac	cag	ggc	cag	tgg	cag	gcc	ggg	aag	cgc	cac	ggc	tac	494
Gly	Gly	Thr	Tyr	Gln	Gly	Gln	Trp	Gln	Ala	Gly	Lys	Arg	His	Gly	Tyr	
126					131					136					141	
ggg	gta	cgc	cag	agt	gtg	ccc	tac	cat	cag	gcg	gcg	ctg	ctg	cgc	tcg	542
Gly	Val	Arg	Gln	Ser	Val	Pro	Tyr	His	Gln	Ala	Ala	Leu	Leu	Arg	Ser	
142					147					152					157	
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Pro	Arg	Arg	Thr	Ser	Leu	Asp	Ser	Gly	His	Ser	Asp	Pro	Pro	Thr	Pro	
158					163					168					173	
ccc	ccg	ccc	ctg	ccc	ttg	ccg	ggc	gac	gag	gga	ggc	agc	ccc	gcc	tcg	638
Pro	Pro	Pro	Leu	Pro	Leu	Pro	Gly	Asp	Glu	Gly	Gly	Ser	Pro	Ala	Ser	
174					179					184					189	
ggc	tcc	cgg	ggc	ggc	ttc	gtg	ctg	gcc	ggg	ccc	ggg	gac	gcc	gac	ggc	686
Gly	Ser	Arg	Gly	Gly	Phe	Val	Leu	Ala	Gly	Pro	Gly	Asp	Ala	Asp	Gly	
190					195					200					205	
gcg	tcg	tcc	cga	aag	cgc	act	ccg	gcg	gcc	ggc	gga	ttc	ttt	cgc	cgt	734
Ala	Ser	Ser	Arg	Lys	Arg	Thr	Pro	Ala	Ala	Gly	Gly	Phe	Phe	Arg	Arg	
206					211					216					221	
tcg	ctg	ctg	ctc	agc	ggg	ctc	cga	gcg	ggc	gga	cgt	cgc	agc	tcc	ctg	782
Ser	Leu	Leu	Leu	Ser	Gly	Leu	Arg	Ala	Gly	Gly	Arg	Arg	Ser	Ser	Leu	
222					227					232					237	
ggc	agc	aag	cga	ggc	tcc	ctg	cgc	agc	gag	gtg	agc	agc	gag	gtg	ggc	830
Gly	Ser	Lys	Arg	Gly	Ser	Leu	Arg	Ser	Glu	Val	Ser	Ser	Glu	Val	Gly	
238					243					248					253	
agc	acc	gga	ccg	ccc	ggc	tcg	gag	gcc	agc	ggg	ccc	ccg	gcc	gca	gcg	878
Ser	Thr	Gly	Pro	Pro	Gly	Ser	Glu	Ala	Ser	Gly	Pro	Pro	Ala	Ala	Ala	
254					259					264					269	
ccg	ccc	gcc	ctc	atc	gag	ggc	tcg	gcc	aca	gag	gtg	tac	gcg	ggc	gag	926
Pro	Pro	Ala	Leu	Ile	Glu	Gly	Ser	Ala	Thr	Glu	Val	Tyr	Ala	Gly	Glu	
270					275					280					285	
tgg	cgc	gca	gat	cgg	cgc	agc	ggc	ttc	ggc	gtc	agc	cag	cgc	tcc	aac	974
Trp	Arg	Ala	Asp	Arg	Arg	Ser	Gly	Phe	Gly	Val	Ser	Gln	Arg	Ser	Asn	
286					291					296					301	
ggg	ctg	cgc	tac	gag	ggc	gag	tgg	ctg	ggc	aac	cgg	cgg	cac	ggc	tac	1022
Gly	Leu	Arg	Tyr	Glu	Gly	Glu	Trp	Leu	Gly	Asn	Arg	Arg	His	Gly	Tyr	
302					307					312					317	
ggg	cgc	acc	acc	cgc	ccc	gac	ggc	tcc	cgc	gag	gag	ggc	aag	tac	aag	1070
Gly	Arg	Thr	Thr	Arg	Pro	Asp	Gly	Ser	Arg	Glu	Glu	Gly	Lys	Tyr	Lys	



gcc cca gca ggc acg gag cct gag ccc atc gcc atg ctg gtc ctg agg	1790
Ala Pro Ala Gly Thr Glu Pro Glu Pro Ile Ala Met Leu Val Leu Arg	
558 563 568 573	
ggc tcg tcc tcg agg ggt cct gat gct ggg tgc ctg aca gaa gag ctc	1838
Gly Ser Ser Ser Arg Gly Pro Asp Ala Gly Cys Leu Thr Glu Glu Leu	
574 579 584 589	
ggg gag ccc gct gca acc gag agg cct gcc cag ccg gga gct gcc aac	1886
Gly Glu Pro Ala Ala Thr Glu Arg Pro Ala Gln Pro Gly Ala Ala Asn	
590 595 600 605	
ccc ctg gtg gtg gga gcc gtg gcc ctc ctg gac ctc agc ctg gca ttc	1934
Pro Leu Val Val Gly Ala Val Ala Leu Leu Asp Leu Ser Leu Ala Phe	
606 611 616 621	
ctg ttc tcc cag ctc ctc acc tga ggctacttcc tggcctgggt ctggctttgg	1988
Leu Phe Ser Gln Leu Leu Thr *	
622 627	
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gagaaggga gtgaaaagta gagtaactcc ccagcatttc cctctttttc tcctcatcg	2648
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caaggcccc acatcccaac tctgggagtt gtggtgggag gaggcacttc tgggggatag	2948
gaccagacaa gataacagga gctcacatgg aagcagaagc tgtgacaagt ttagtagtcc	3008
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    Met Ser Thr Ala Ala Phe His Ile Ser Ser Leu Leu Glu Lys Met
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acg tcc agc gac aag gac ttc agg ttc atg gcc acc agc gac ctg atg      154
Thr Ser Ser Asp Lys Asp Phe Arg Phe Met Ala Thr Ser Asp Leu Met
  16             21             26             31

tcg gag ttg cag aag gac tcc atc cag ctg gac gag gac agc gag cgc      202
Ser Glu Leu Gln Lys Asp Ser Ile Gln Leu Asp Glu Asp Ser Glu Arg
  32             37             42             47

aag gtg gtg aag atg ctg ctc cgg ctc ctg gag gac aag aac ggt gag      250
Lys Val Val Lys Met Leu Leu Arg Leu Leu Glu Asp Lys Asn Gly Glu
  48             53             58             63

gtg cag aac ctg gct gtc aag tgg ctg ggt gtc ccg ctg ggc gcc ttc      298
Val Gln Asn Leu Ala Val Lys Trp Leu Gly Val Pro Leu Gly Ala Phe
  64             69             74             79

cac gcc agc ctc ctg cac tgt ctg ctg cca cag ctg agc agc ccg cgc      346
His Ala Ser Leu Leu His Cys Leu Leu Pro Gln Leu Ser Ser Pro Arg
  80             85             90             95

ctg gcg gtg cgc aag cgg gcg gtc gga gcg ctt ggc cac ctg gcg gcc      394
Leu Ala Val Arg Lys Arg Ala Val Gly Ala Leu Gly His Leu Ala Ala
  96             101            106            111

gcc tgc agc acc gac ctc ttc gtc gag ctc gct gac cac cta ctg gac      442
Ala Cys Ser Thr Asp Leu Phe Val Glu Leu Ala Asp His Leu Leu Asp
 112             117            122            127

cgg ctg ccc ggc ccg cgg gtg ccc acc agc ccg act gcc atc cgc acc      490
Arg Leu Pro Gly Pro Arg Val Pro Thr Ser Pro Thr Ala Ile Arg Thr
 128             133            138            143

ctg atc caa tgt ttg ggc agc gtc ggc cgc cag gcc ggc cac cgc ctc      538
Leu Ile Gln Cys Leu Gly Ser Val Gly Arg Gln Ala Gly His Arg Leu
 144             149            154            159

ggg gct cac ctg gac cgc ctg gtg ccc ctg gtg gag gat ttc tgc aac      586
Gly Ala His Leu Asp Arg Leu Val Pro Leu Val Glu Asp Phe Cys Asn

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ttc ttg agg aag tgc	ccc aag gaa atg ggt	cct cac gtg ccc aac	gtg	682
Phe Leu Arg Lys Cys	Pro Lys Glu Met Gly	Pro His Val Pro Asn	Val	
192	197	202	207	
acc agc ctc tgc ctc	caa tac ata aaa cac	gac ccc aac tac aac	tac	730
Thr Ser Leu Cys Leu	Gln Tyr Ile Lys His	Asp Pro Asn Tyr Asn	Tyr	
208	213	218	223	
gac agt gat gag gat	gag gag cag atg gag	aca gag gat agt gaa	ttc	778
Asp Ser Asp Glu Asp	Glu Glu Gln Met Glu	Thr Glu Asp Ser Glu	Phe	
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Ser Glu Gln Glu Ser	Glu Asp Glu Tyr Ser	Asp Asp Asp Asp Met	Ser	
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tgg aag gtg cgc cgg	gca gct gcc aag tgc	atc gca gcc ttg atc	agc	874
Trp Lys Val Arg Arg	Ala Ala Ala Lys Cys	Ile Ala Ala Leu Ile	Ser	
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tcg cgg cct gac ctg	ctg ccc gat ttc cac	tgc acc ctg gca cct	gtg	922
Ser Arg Pro Asp Leu	Leu Pro Asp Phe His	Cys Thr Leu Ala Pro	Val	
272	277	282	287	
ctc atc cgc cgc ttc	aaa gaa cgc gag gag	aac gtc aag gct gac	gtc	970
Leu Ile Arg Arg Phe	Lys Glu Arg Glu Glu	Asn Val Lys Ala Asp	Val	
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ttc act gct tac atc	gtg ctg ctg cgg caa	aca cgg ccc ccg aag	gga	1018
Phe Thr Ala Tyr Ile	Val Leu Leu Arg Gln	Thr Arg Pro Pro Lys	Gly	
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Trp Leu Glu Ala Met	Glu Glu Pro Thr Gln	Thr Gly Ser Asn Leu	His	
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atg cta cgt gga cag	gtg ccc ctt gtg gtc	aag gcc ctg cag cgg	cag	1114
Met Leu Arg Gly Gln	Val Pro Leu Val Val	Lys Ala Leu Gln Arg	Gln	
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Leu Lys Asp Arg Ser	Val Arg Ala Arg Gln	Gly Cys Phe Ser Leu	Leu	
352	357	362	367	
acc gag ctg gcg ggt	gtc ctc cca ggc agc	ctg gcc gag cat atg	cct	1210
Thr Glu Leu Ala Gly	Val Leu Pro Gly Ser	Leu Ala Glu His Met	Pro	
368	373	378	383	
gtg ctg gta tca ggc	atc atc ttc tcg ctg	gcc gac cgc tcc agc	tcc	1258
Val Leu Val Ser Gly	Ile Ile Phe Ser Leu	Ala Asp Arg Ser Ser	Ser	
384	389	394	399	

tcc acc atc cgg atg gat gcc ctg gcc ttc ttg cag ggg ctg ctg ggc Ser Thr Ile Arg Met Asp Ala Leu Ala Phe Leu Gln Gly Leu Leu Gly 400 405 410 415	1306
acc gaa cca gct gag gcc ttc cac cca cac ttg cct atc ctc ctg cca Thr Glu Pro Ala Glu Ala Phe His Pro His Leu Pro Ile Leu Leu Pro 416 421 426 431	1354
cct gtg atg gcc tgt gtg gct gac tct ttc tac aag att gca gcc gag Pro Val Met Ala Cys Val Ala Asp Ser Phe Tyr Lys Ile Ala Ala Glu 432 437 442 447	1402
gcc ctg gtg gtg ctg cag gag ctg gtg cgg gcc ctg tgg ccg ctg cac Ala Leu Val Val Leu Gln Glu Leu Val Arg Ala Leu Trp Pro Leu His 448 453 458 463	1450
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gtc acc ctg gcg cga ctt cgt gcc act gac ctg gac cag gag gtg aag Val Thr Leu Ala Arg Leu Arg Ala Thr Asp Leu Asp Gln Glu Val Lys 480 485 490 495	1546
gag cgg gcc att tcc tgc atg ggc cac ctt gta ggc cac ctg ggt gac Glu Arg Ala Ile Ser Cys Met Gly His Leu Val Gly His Leu Gly Asp 496 501 506 511	1594
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gcc ctg gtc aac gag agc gac atg cat gtg gcc cag ctg gct gtg gac Ala Leu Val Asn Glu Ser Asp Met His Val Ala Gln Leu Ala Val Asp 608 613 618 623	1930



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ccc	cgc	ttg	cgg	aag	cag	ctt	gct	gca	ggc	cgg	cca	cac	acc	cgg	agc	2746
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Thr	Val	Ile	Thr	Ala	Val	Lys	Phe	Leu	Ile	Ser	Asp	Gln	Pro	His	Pro	
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Ile	Asp	Pro	Leu	Leu	Lys	Ser	Phe	Ile	Ala	Val	His	Asn	Lys	Pro	Ser	
912					917					922					927	
cta	gtc	cgg	gac	ctg	ctg	gat	gac	atc	ctg	ccc	ctc	ctc	tac	cag	gag	2890
Leu	Val	Arg	Asp	Leu	Leu	Asp	Asp	Ile	Leu	Pro	Leu	Leu	Tyr	Gln	Glu	
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944					949					954					959	
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Lys	His	Thr	Val	Asp	Asp	Gly	Leu	Asp	Val	Arg	Lys	Ala	Ala	Phe	Glu	
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Cys	Met	Tyr	Ser	Leu	Leu	Glu	Ser	Cys	Leu	Gly	Gln	Leu	Asp	Ile	Cys	
976					981					986					991	
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Glu	Phe	Leu	Asn	His	Val	Glu	Asp	Gly	Leu	Lys	Asp	His	Tyr	Asp	Ile	
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Ala	Pro	Val	Leu	Gln	Arg	Val	Asp	Arg	Leu	Ile	Glu	Pro	Leu	Arg	Ala	
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Ser Glu Leu Gln Lys Asp Ser Ile Gln Leu Asp Glu Asp Ser Glu Arg			
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48 53 58 63			
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64 69 74 79			
cac gcc agc ctc ctg cac tgt ctg ctg cca cag ctg agc agc ccg cgc	346		
His Ala Ser Leu Leu His Cys Leu Leu Pro Gln Leu Ser Ser Pro Arg			
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Leu Ala Val Arg Lys Arg Ala Val Gly Ala Leu Gly His Leu Ala Ala			
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Ala Cys Ser Thr Asp Leu Phe Val Glu Leu Ala Asp His Leu Leu Asp			
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Arg Leu Pro Gly Pro Arg Val Pro Thr Ser Pro Thr Ala Ile Arg Thr			
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Leu Ile Gln Cys Leu Gly Ser Val Gly Arg Gln Ala Gly His Arg Leu			
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Phe Leu Arg Lys Cys Pro Lys Glu Met Gly Pro His Val Pro Asn Val			
192 197 202 207			
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Asp Ser Asp Glu Asp Glu Glu Gln Met Glu Thr Glu Asp Ser Glu Phe			
224 229 234 239			

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Pro Val Met Ala Cys Val Ala Asp Ser Phe Tyr Lys Ile Ala Ala Glu	
432 437 442 447	
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Ala Leu Val Val Leu Gln Glu Leu Val Arg Ala Leu Trp Pro Leu His	
448 453 458 463	





Leu	Thr	Ala	Pro	Val	Tyr	Glu	Gln	Ala	Val	Asp	Gly	Gly	Pro	Gly	Leu	
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His	Lys	Gln	Val	Phe	His	Ser	Leu	Ala	Arg	Cys	Val	Ala	Ala	Leu	Ser	
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Val	Arg	Ala	Ala	Ala	Ser	Tyr	Ala	Leu	Gly	Arg	Val	Gly	Ala	Gly	Ser	
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880					885					890					895	
acc	gtc	atc	aca	gcg	gtc	aag	ttc	ctt	atc	tcg	gac	cag	ccc	cat	ccc	2794
Thr	Val	Ile	Thr	Ala	Val	Lys	Phe	Leu	Ile	Ser	Asp	Gln	Pro	His	Pro	
896					901					906					911	
att	gac	ccc	ctc	ctg	aag	agc	ttc	atc	gga	gag	ttc	atg	gag	agc	ctg	2842
Ile	Asp	Pro	Leu	Leu	Lys	Ser	Phe	Ile	Gly	Glu	Phe	Met	Glu	Ser	Leu	

912	917	922	927	
cag gac cca gac ctg aac gtg cgc cgt gcg act ctg gct ttc ttc aac				2890
Gln Asp Pro Asp Leu Asn Val Arg Arg Ala Thr Leu Ala Phe Phe Asn				
928	933	938	943	
tca gct gtg cac aac aag ccc tcg cta gtc cgg gac ctg ctg gat gac				2938
Ser Ala Val His Asn Lys Pro Ser Leu Val Arg Asp Leu Leu Asp Asp				
944	949	954	959	
atc ctg ccc ctc ctc tac cag gag aca aag atc cgg cgg gac ctc atc				2986
Ile Leu Pro Leu Leu Tyr Gln Glu Thr Lys Ile Arg Arg Asp Leu Ile				
960	965	970	975	
cga gag gtg gag atg ggg ccc ttt aaa cat aca gtg gac gat ggg ctg				3034
Arg Glu Val Glu Met Gly Pro Phe Lys His Thr Val Asp Asp Gly Leu				
976	981	986	991	
gac gtg cgg aag gcg gcc ttt gaa tgc atg tat tca ctg ctt gag agc				3082
Asp Val Arg Lys Ala Ala Phe Glu Cys Met Tyr Ser Leu Leu Glu Ser				
992	997	1002	1007	
tgc ctg ggc cag ctg gat atc tgt gag ttc ctg aac cat gtg gag gac				3130
Cys Leu Gly Gln Leu Asp Ile Cys Glu Phe Leu Asn His Val Glu Asp				
1008	1013	1018	1023	
ggg ctg aag gac cac tac gac atc cgg atg ctg acc ttc atc atg gtt				3178
Gly Leu Lys Asp His Tyr Asp Ile Arg Met Leu Thr Phe Ile Met Val				
1024	1029	1034	1039	
gcc cgg ctg gcc acc ctg tgt cct gca cct gtc ctg cag agg gtg gac				3226
Ala Arg Leu Ala Thr Leu Cys Pro Ala Pro Val Leu Gln Arg Val Asp				
1040	1045	1050	1055	
cga ctc att gag cca cta agg gcc acc tgc act gcc aag gtc aaa gct				3274
Arg Leu Ile Glu Pro Leu Arg Ala Thr Cys Thr Ala Lys Val Lys Ala				
1056	1061	1066	1071	
ggt tct gtg aag cag gag ttt gaa aag caa gat gaa ctg aag cgc tct				3322
Gly Ser Val Lys Gln Glu Phe Glu Lys Gln Asp Glu Leu Lys Arg Ser				
1072	1077	1082	1087	
gca atg agg gca gtg gct gcc ctg ctg acc atc ccc gag gtg ggg aaa				3370
Ala Met Arg Ala Val Ala Ala Leu Leu Thr Ile Pro Glu Val Gly Lys				
1088	1093	1098	1103	
agc ccc atc atg gcc gac ttc tct tcc caa atc aga tcc aac cct gaa				3418
Ser Pro Ile Met Ala Asp Phe Ser Ser Gln Ile Arg Ser Asn Pro Glu				
1104	1109	1114	1119	
ctt gct gcc ctc ttt gaa agc atc cag aag gat tcc act tca gcc ccc				3466
Leu Ala Ala Leu Phe Glu Ser Ile Gln Lys Asp Ser Thr Ser Ala Pro				
1120	1125	1130	1135	
agc aca gac tca atg gag ctc agc tag tcccc tcagcaccaa ggtgggacct				3518
Ser Thr Asp Ser Met Glu Leu Ser *				
1136	1141			



Asp 30	His	Ala	Asp	Ile	Ser 35	Asn	Cys	Gly	Asn	Ser 40	Phe	Gln	Leu	Val	Ser 45	
gaa 46	ggt	gct	tcc	tgg	agg 51	ggc	ctg	ccc	cac	tgt 56	tcc	tgt	gct	gag	ttc 61	372
Glu	Gly	Ala	Ser	Trp	Arg	Gly	Leu	Pro	His	Cys	Ser	Cys	Ala	Glu	Phe	
cag 62	gac	agc	ctc	aac	ttc 67	agc	tac	cat	ccc	tca 72	ggc	ctg	agc	ctg	cac 77	420
Gln	Asp	Ser	Leu	Asn	Phe	Ser	Tyr	His	Pro	Ser	Gly	Leu	Ser	Leu	His	
ctc 78	aga	cca	ccc	agt	cgg 83	gga	aac	tcc	ccc	aag 88	gag	cag	ccc	ttc	tcc 93	468
Leu	Arg	Pro	Pro	Ser	Arg	Gly	Asn	Ser	Pro	Lys	Glu	Gln	Pro	Phe	Ser	
caa 94	gtc	cta	aga	cct	gag 99	ccc	cca	gat	cca	gag 104	aag	ctt	cct	gtg	ccc 109	516
Gln	Val	Leu	Arg	Pro	Glu	Pro	Pro	Asp	Pro	Glu	Lys	Leu	Pro	Val	Pro	
cct 110	gcc	cct	cca	tcc	aag 115	agg	cac	tgc	cgc	tca 120	ctc	tca	gtg	ccc	gtg 125	564
Pro	Ala	Pro	Pro	Ser	Lys	Arg	His	Cys	Arg	Ser	Leu	Ser	Val	Pro	Val	
gac 126	ctg	tct	cgc	tgg	cag 131	ccg	gtg	tgg	cgg	ccc 136	gcc	ccc	tcc	aag	ctg 141	612
Asp	Leu	Ser	Arg	Trp	Gln	Pro	Val	Trp	Arg	Pro	Ala	Pro	Ser	Lys	Leu	
tgg 142	act	ccc	ata	aag	cac 147	cgg	ggc	agt	ggc	gga 152	ggg	ggc	ggg	ccg	cag 157	660
Trp	Thr	Pro	Ile	Lys	His	Arg	Gly	Ser	Gly	Gly	Gly	Gly	Gly	Pro	Gln	
gtg 158	cct	cac	cag	agc	ccc 163	cca	aag	cgg	gtc	tcc 168	agc	ctc	agg	ttc	ctc 173	708
Val	Pro	His	Gln	Ser	Pro	Pro	Lys	Arg	Val	Ser	Ser	Leu	Arg	Phe	Leu	
caa 174	gct	ccc	agt	gcc	tct 179	tct	caa	tgt	gcc	cca 184	gct	cac	aga	ccc	tac 189	756
Gln	Ala	Pro	Ser	Ala	Ser	Ser	Gln	Cys	Ala	Pro	Ala	His	Arg	Pro	Tyr	
agc 190	cct	cct	ttc	ttc	agc 195	ctg	gcc	ctg	gcc	caa 200	gat	tcc	tct	cga	ccc 205	804
Ser	Pro	Pro	Phe	Phe	Ser	Leu	Ala	Leu	Ala	Gln	Asp	Ser	Ser	Arg	Pro	
tgc 206	gcc	gcc	tcc	cct	caa 211	agt	ggc	tcc	tgg	gag 216	agt	gat	gct	gag	tcc 221	852
Cys	Ala	Ala	Ser	Pro	Gln	Ser	Gly	Ser	Trp	Glu	Ser	Asp	Ala	Glu	Ser	
ttg 222	tca	cct	tgc	cca	cct 227	cag	cgc	cgc	ttc	tcc 232	ctg	tca	ccc	agt	ctg 237	900
Leu	Ser	Pro	Cys	Pro	Pro	Gln	Arg	Arg	Phe	Ser	Leu	Ser	Pro	Ser	Leu	
ggc 238	ccg	cag	gca	agc	cgc 243	ttc	ttg	ccc	tct	gcc 248	cgg	agc	tct	ccc	gca 253	948
Gly	Pro	Gln	Ala	Ser	Arg	Phe	Leu	Pro	Ser	Ala	Arg	Ser	Ser	Pro	Ala	
tcc 244	tcc	cca	gag	ctg	ccc 249	tgg	cga	cct	cga	ggc 254	ctc	cgc	aac	ctt	ccc 259	996
Ser	Ser	Pro	Glu	Leu	Pro	Trp	Arg	Pro	Arg	Gly	Leu	Arg	Asn	Leu	Pro	

254	259	264	269	
cga agc cgc tca cag cct tgt gat ctg gat gcc cgc aaa act ggg gtc				1044
Arg Ser Arg Ser Gln Pro Cys Asp Leu Asp Ala Arg Lys Thr Gly Val				
270	275	280	285	
aag cgg cgc cac gag gaa gac ccc cgg cgt ctg cgg cct tcg ttg gac				1092
Lys Arg Arg His Glu Glu Asp Pro Arg Arg Leu Arg Pro Ser Leu Asp				
286	291	296	301	
ttt gac aag atg aat cag aaa cca tac tca gga ggt ctt tgt ctc caa				1140
Phe Asp Lys Met Asn Gln Lys Pro Tyr Ser Gly Gly Leu Cys Leu Gln				
302	307	312	317	
gaa aca gcc cgg gaa ggc agc agc atc tct cca cca tgg ttc atg gcc				1188
Glu Thr Ala Arg Glu Gly Ser Ser Ile Ser Pro Pro Trp Phe Met Ala				
318	323	328	333	
tgt agc ccc cca ccc ctc tct gct tcc tgc agc ccc act ggg ggt tcc				1236
Cys Ser Pro Pro Pro Leu Ser Ala Ser Cys Ser Pro Thr Gly Gly Ser				
334	339	344	349	
tcc cag gtg ctg agt gaa agc gaa gag gag gag gag ggg gct gtg cgg				1284
Ser Gln Val Leu Ser Glu Ser Glu Glu Glu Glu Glu Gly Ala Val Arg				
350	355	360	365	
tgg ggt cgg cag gcg ctg agc aag cgg aca ctg tgc cag cgg gac ttt				1332
Trp Gly Arg Gln Ala Leu Ser Lys Arg Thr Leu Cys Gln Arg Asp Phe				
366	371	376	381	
ggg gac ctg gac ttg aat ttg att gag gaa aac taa aact gagaggctac				1382
Gly Asp Leu Asp Leu Asn Leu Ile Glu Glu Asn *				
382	387	392		
ttcctgggaa aaaaaaaaaa aaaaaaa				1409

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ccgcctccg ccgtgcctc ctccgcccg gccgttcgct gctgcgcggg gagagcgagg	120
cggggccgcc ggggcccgc atg gag ccc gac tcg gtg att gag gac aag acc	172
Met Glu Pro Asp Ser Val Ile Glu Asp Lys Thr	

1

5



Arg 236	Ser	Glu	Asn	Ser	Lys 241	Gly	Val	Tyr	Cys	Leu 246	Gln	Tyr	Asp	Asp	Glu 251	
aaa 252	att Ile	atc Ile	agt Ser	ggc Gly	cta Leu 257	cga Arg	gat Asp	aat Asn	tct Ser	att Ile 262	aag Lys	ata Ile	tgg Trp	gat Asp	aaa Lys 267	940
acc 268	agc Ser	ctg Leu	gaa Glu	tgt Cys	ttg Leu 273	aaa Lys	gtg Val	tta Leu	aca Thr	gga Gly 278	cac His	aca Thr	ggc Gly	tct Ser	gtc Val 283	988
ctc 284	tgt Cys	ctg Leu	cag Gln	tat Tyr	gat Asp 289	gag Glu	cgt Arg	gtc Val	att Ile	gta Val 294	act Thr	ggc Gly	tct Ser	tca Ser	gat Asp 299	1036
tct 300	acg Thr	gtg Val	aga Arg	gtg Val	tgg Trp 305	gat Asp	gtg Val	aac Asn	acg Thr	ggg Gly 310	gaa Glu	gtt Val	ctt Leu	aac Asn	aca Thr 315	1084
ttg 316	atc Ile	cac His	cac His	aat Asn	gag Glu 321	gct Ala	gta Val	ttg Leu	cac His	tta Leu 326	cgc Arg	ttc Phe	agc Ser	aat Asn	gga Gly 331	1132
ctg 332	atg Met	gtg Val	acc Thr	tgt Cys	tcc Ser 337	aag Lys	gac Asp	cgc Arg	tcc Ser	att Ile 342	gct Ala	gtg Val	tgg Trp	gac Asp	atg Met 347	1180
gct 348	tct Ser	gcg Ala	acc Thr	gac Asp	atc Ile 353	act Thr	tta Leu	cgc Arg	cgt Arg	gtc Val 358	ctg Leu	gtt Val	ggc Gly	cac His	cgg Arg 363	1228
gct 364	gcc Ala	gtc Val	aat Asn	gta Val	gta Val 369	gac Asp	ttt Phe	gac Asp	gac Asp	aag Lys 374	tac Tyr	atc Ile	gtg Val	tct Ser	gcc Ala 379	1276
tct 380	ggg Ser	gac Asp	agg Arg	acc Thr	atc Ile 385	aaa Lys	gtc Val	tgg Trp	agc Ser	acg Thr 390	agc Ser	acc Thr	tgt Cys	gaa Glu	ttt Phe 395	1324
gtt 396	cgt Arg	act Thr	ctc Leu	aat Asn	ggg Gly 401	cac His	aag Lys	cgg Arg	ggc Gly	att Ile 406	gcc Ala	tgt Cys	ctc Leu	cag Gln	tac Tyr 411	1372
agg 412	gat Asp	cgc Arg	ctg Leu	gtt Val	gtt Val 417	agt Ser	gga Gly	tca Ser	tca Ser	gat Asp 422	aat Asn	acc Thr	att Ile	agg Arg	ctc Leu 427	1420
tgg 428	gat Trp	att Asp	gaa Ile	tgt Cys	ggg Gly 433	gcc Ala	tgt Cys	tta Leu	aga Arg	gtc Val 438	cta Leu	gag Glu	gga Gly	cat His	gaa Glu 443	1468
gaa 444	ttg Leu	gtc Val	cga Arg	tgc Cys	atc Ile 449	cgg Arg	ttt Phe	gat Asp	aac Asn	aag Lys 454	agg Arg	att Ile	gtc Val	agt Ser	ggg Gly 459	1516
gcc Ala	tat Tyr	gat Asp	ggg Gly	aaa Lys	att Ile	aaa Lys	gtt Val	tgg Trp	gac Asp	ttg Leu	caa Gln	gct Ala	gct Ala	ctt Leu	gac Asp	1564







<213> Homo sapiens

<220>

<221> CDS

<222> (76) .. (2907)

<400> 40

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ggcagcccat ggagg atg gat ggg agc acg gag agg ctg gag gca agg aga 111  
Met Asp Gly Ser Thr Glu Arg Leu Glu Ala Arg Arg  
1 5 10

cca gcc ggg agg ctg ccg tgg tca tcc agg caa gaa atg acg agg cgt 159  
Pro Ala Gly Arg Leu Pro Trp Ser Ser Arg Gln Glu Met Thr Arg Arg  
13 18 23 28

ccc tcc ctg atg gcg ggc aga cag cac gga tgg agc gcc cag cag agt 207  
Pro Ser Leu Met Ala Gly Arg Gln His Gly Trp Ser Ala Gln Gln Ser  
29 34 39 44

gcc acc gtg gcc aac cca gtg cct ggt gcc aac ccg gac ctg ctt ccc 255  
Ala Thr Val Ala Asn Pro Val Pro Gly Ala Asn Pro Asp Leu Leu Pro  
45 50 55 60

cac ttc ctg gtg gag ccc gag gat gtg tac atc gtc aag aac aag cca 303  
His Phe Leu Val Glu Pro Glu Asp Val Tyr Ile Val Lys Asn Lys Pro  
61 66 71 76

gtg ctg ctt gtg tgc aag gcc gtg ccc gcc acg cag atc ttc ttc aag 351  
Val Leu Leu Val Cys Lys Ala Val Pro Ala Thr Gln Ile Phe Phe Lys  
77 82 87 92

tgc aac ggg gag tgg gtg cgc cag gtg gac cac gtg atc gag cgc agc 399  
Cys Asn Gly Glu Trp Val Arg Gln Val Asp His Val Ile Glu Arg Ser  
93 98 103 108

aca gac ggg agc agt ggg ctg ccc acc atg gag gtc cgc att aat gtc 447  
Thr Asp Gly Ser Ser Gly Leu Pro Thr Met Glu Val Arg Ile Asn Val  
109 114 119 124

tca agg cag cag gtc gag aag gtg ttc ggg ctg gag gaa tac tgg tgc 495  
Ser Arg Gln Gln Val Glu Lys Val Phe Gly Leu Glu Glu Tyr Trp Cys  
125 130 135 140

cag tgc gtg gca tgg agc tcc tcg ggc acc acc aag agt cag aag gcc 543  
Gln Cys Val Ala Trp Ser Ser Ser Gly Thr Thr Lys Ser Gln Lys Ala  
141 146 151 156

tac atc cgc ata gcc tat ttg cgc aag aac ttc gag cag gag ccg ctg 591  
Tyr Ile Arg Ile Ala Tyr Leu Arg Lys Asn Phe Glu Gln Glu Pro Leu  
157 162 167 172

gcc aag gag gtg tcc ctg gag cag ggc atc gtg ctg ccc tgc cgt cca 639  
Ala Lys Glu Val Ser Leu Glu Gln Gly Ile Val Leu Pro Cys Arg Pro  
173 178 183 188





637		642		647		652	
gag gag gcg ccc tcc cac ctc tac tac tgc cag ctg gag gcc agt gcc	2079						
Glu Glu Ala Pro Ser His Leu Tyr Tyr Cys Gln Leu Glu Ala Ser Ala							
653		658		663		668	
tgc tac gtc ttc acc gag cag ctg ggc cgc ttt gcc ctg gtg gga gag	2127						
Cys Tyr Val Phe Thr Glu Gln Leu Gly Arg Phe Ala Leu Val Gly Glu							
669		674		679		684	
gcc ctc agc gtg gct gcc gcc aag cgc ctc aag ctg ctt ctg ttt gcg	2175						
Ala Leu Ser Val Ala Ala Ala Lys Arg Leu Lys Leu Leu Leu Phe Ala							
685		690		695		700	
ccg gtg gcc tgc acc tcc ctc gag tac aac atc cgg gtc tac tgc ctg	2223						
Pro Val Ala Cys Thr Ser Leu Glu Tyr Asn Ile Arg Val Tyr Cys Leu							
701		706		711		716	
cat gac acc cac gat gca ctc aag gag gtg gtg cag ctg gag aag cag	2271						
His Asp Thr His Asp Ala Leu Lys Glu Val Val Gln Leu Glu Lys Gln							
717		722		727		732	
ctg ggg gga cag ctg atc cag gag cca cgg gtc ctg cac ttc aag gac	2319						
Leu Gly Gly Gln Leu Ile Gln Glu Pro Arg Val Leu His Phe Lys Asp							
733		738		743		748	
agt tac cac aac ctg cgc cta tcc atc cac gat gtg ccc agc tcc ctg	2367						
Ser Tyr His Asn Leu Arg Leu Ser Ile His Asp Val Pro Ser Ser Leu							
749		754		759		764	
tgg aag agt aag ctc ctt gtc agc tac cag gag atc ccc ttt tat cac	2415						
Trp Lys Ser Lys Leu Leu Val Ser Tyr Gln Glu Ile Pro Phe Tyr His							
765		770		775		780	
atc tgg aat ggc acg cag cgg tac ttg cac tgc acc ttc acc ctg gag	2463						
Ile Trp Asn Gly Thr Gln Arg Tyr Leu His Cys Thr Phe Thr Leu Glu							
781		786		791		796	
cgt gtc agc ccc agc act agt gac ctg gcc tgc aag ctg tgg gtg tgg	2511						
Arg Val Ser Pro Ser Thr Ser Asp Leu Ala Cys Lys Leu Trp Val Trp							
797		802		807		812	
cag gtg gag ggc gac ggg cag agc ttc agc atc aac ttc aac atc acc	2559						
Gln Val Glu Gly Asp Gly Gln Ser Phe Ser Ile Asn Phe Asn Ile Thr							
813		818		823		828	
aag gac aca agg ttt gct gag ctg ctg gct ctg gag agt gaa gcg ggg	2607						
Lys Asp Thr Arg Phe Ala Glu Leu Leu Ala Leu Glu Ser Glu Ala Gly							
829		834		839		844	
gtc cca gcc ctg gtg ggc ccc agt gcc ttc aag atc ccc ttc ctc att	2655						
Val Pro Ala Leu Val Gly Pro Ser Ala Phe Lys Ile Pro Phe Leu Ile							
845		850		855		860	
cgg cag aag ata att tcc agc ctg gac cca ccc tgt agg cgg ggt gcc	2703						
Arg Gln Lys Ile Ile Ser Ser Leu Asp Pro Pro Cys Arg Arg Gly Ala							
861		866		871		876	





Lys 287	Lys	Pro	Glu	Pro	Cys 292	Lys	Pro	Ile	Leu	Lys 297	Val	Glu	Phe	Lys	Thr 302	
act 303	aga	tct	ggg	gag	cct 308	ttt	att	att	tta	tca 313	gga	ggt	ttg	tca	tat 318	1140
Thr	Arg	Ser	Gly	Glu	Pro	Phe	Ile	Ile	Leu	Ser	Gly	Gly	Leu	Ser	Tyr	
gat 319	act	gta	gga	aga	aga 324	cct	tgc	tta	aca	gtg 329	atg	cat	ggg	aaa	agc 334	1188
Asp	Thr	Val	Gly	Arg	Arg	Pro	Cys	Leu	Thr	Val	Met	His	Gly	Lys	Ser	
act 335	gct	gtg	cta	gaa	atg 340	gac	tat	tca	att	gtc 345	gat	ttt	cta	acg	ctg 350	1236
Thr	Ala	Val	Leu	Glu	Met	Asp	Tyr	Ser	Ile	Val	Asp	Phe	Leu	Thr	Leu	
tgt 351	gaa	aca	cca	tac	cca 356	aat	gat	ttt	caa	gaa 361	cca	tat	gct	gtg	gtt 366	1284
Cys	Glu	Thr	Pro	Tyr	Pro	Asn	Asp	Phe	Gln	Glu	Pro	Tyr	Ala	Val	Val	
gtt 367	ctt	cta	gaa	aag	gat 372	tta	gta	ctt	ata	gac 377	ctt	gca	caa	aat	gga 382	1332
Val	Leu	Leu	Glu	Lys	Asp	Leu	Val	Leu	Ile	Asp	Leu	Ala	Gln	Asn	Gly	
tat 383	cct	ata	ttt	gaa	aat 388	ccc	tac	cct	ttg	agt 393	ata	cat	gag	tcc	cct 398	1380
Tyr	Pro	Ile	Phe	Glu	Asn	Pro	Tyr	Pro	Leu	Ser	Ile	His	Glu	Ser	Pro	
gtt 399	aca	tgt	tgc	gaa	tat 404	ttt	gcg	gat	tgt	cct 409	gtg	gac	ctt	att	cct 414	1428
Val	Thr	Cys	Cys	Glu	Tyr	Phe	Ala	Asp	Cys	Pro	Val	Asp	Leu	Ile	Pro	
gca 415	ctt	tat	tct	gtt	gga 420	gct	aga	cag	aaa	cgt 425	caa	ggt	tac	agc	aaa 430	1476
Ala	Leu	Tyr	Ser	Val	Gly	Ala	Arg	Gln	Lys	Arg	Gln	Gly	Tyr	Ser	Lys	
aag 431	gaa	tgg	ccc	atc	aac 436	gga	ggt	aat	tgg	ggc 441	ttg	ggt	gct	caa	agt 446	1524
Lys	Glu	Trp	Pro	Ile	Asn	Gly	Gly	Asn	Trp	Gly	Leu	Gly	Ala	Gln	Ser	
tac 447	cca	gaa	ata	att	att 452	aca	ggg	cat	gct	gat 457	ggg	tca	gtt	aag	ttc 462	1572
Tyr	Pro	Glu	Ile	Ile	Ile	Thr	Gly	His	Ala	Asp	Gly	Ser	Val	Lys	Phe	
tgg 463	gat	gct	tct	gca	ata 468	act	cta	caa	gta	tta 473	tat	aag	cta	aag	aca 478	1620
Trp	Asp	Ala	Ser	Ala	Ile	Thr	Leu	Gln	Val	Leu	Tyr	Lys	Leu	Lys	Thr	
tct 479	aaa	gta	ttt	gaa	aag 484	tca	aga	aat	aaa	gat 489	gac	agg	cca	aac	aca 494	1668
Ser	Lys	Val	Phe	Glu	Lys	Ser	Arg	Asn	Lys	Asp	Asp	Arg	Pro	Asn	Thr	
gac 495	att	gta	gat	gaa	gat 500	cca	tat	gcc	att	cag 505	atc	atc	tcc	tgg	tgt 510	1716
Asp	Ile	Val	Asp	Glu	Asp	Pro	Tyr	Ala	Ile	Gln	Ile	Ile	Ser	Trp	Cys	
cca 511	gaa	agt	aga	atg	ctg 516	tgc	atc	gct	gga	gtt 521	tca	gct	cat	gtc	att 526	1764
Pro	Glu	Ser	Arg	Met	Leu	Cys	Ile	Ala	Gly	Val	Ser	Ala	His	Val	Ile	



511		516		521		526	
att tat aga ttc agc aag cag gaa gta atc aca gaa gtc att ccg atg							1812
Ile Tyr Arg Phe Ser Lys Gln Glu Val Ile Thr Glu Val Ile Pro Met							
527		532		537		542	
ctt gaa gtt cga tta tta tat gag ata aat gat gtg gaa act ccg gag							1860
Leu Glu Val Arg Leu Leu Tyr Glu Ile Asn Asp Val Glu Thr Pro Glu							
543		548		553		558	
ggt gag cag cca cca cct ttg cca aca ccc gtg gga ggg tcc aac cct							1908
Gly Glu Gln Pro Pro Pro Leu Pro Thr Pro Val Gly Gly Ser Asn Pro							
559		564		569		574	
cag ccc atc cct cct cag tct cat cca tct acc agt agc agt tca tct							1956
Gln Pro Ile Pro Pro Gln Ser His Pro Ser Thr Ser Ser Ser Ser Ser							
575		580		585		590	
gat ggg ctt cgt gat aat gta cct tgt tta aat gta gtg tgt aag gag							2004
Asp Gly Leu Arg Asp Asn Val Pro Cys Leu Asn Val Val Cys Lys Glu							
591		596		601		606	
cat gga aat cat ttt atc tta aca aga agt aaa aag ctg aac aaa ctg							2052
His Gly Asn His Phe Ile Leu Thr Arg Ser Lys Lys Leu Asn Lys Leu							
607		612		617		622	
gaa aat caa caa ctc ttc tta aag atc tgt aag aga aga ctg cct tca							2100
Glu Asn Gln Gln Leu Phe Leu Lys Ile Cys Lys Arg Arg Leu Pro Ser							
623		628		633		638	
gaa ata aca ctt tta cga gag cct aac ctg ctg ggg ttt tat cag gga							2148
Glu Ile Thr Leu Leu Arg Glu Pro Asn Leu Leu Gly Phe Tyr Gln Gly							
639		644		649		654	
cca act aac ctg aga gaa gaa aaa tca ctc cag tgg gcc caa gcc ttc							2196
Pro Thr Asn Leu Arg Glu Glu Lys Ser Leu Gln Trp Ala Gln Ala Phe							
655		660		665		670	
caa gta aag gaa gag aag tac gca act cca gcc cac ttt agc cat ctt							2244
Gln Val Lys Glu Glu Lys Tyr Ala Thr Pro Ala His Phe Ser His Leu							
671		676		681		686	
att cca cct aaa agg gag tgg gag gaa gta aaa gaa cca gtg gaa ttt							2292
Ile Pro Pro Lys Arg Glu Trp Glu Glu Val Lys Glu Pro Val Glu Phe							
687		692		697		702	
gaa ata att aat ttg aaa tta ttt gaa att tat att agc acc cca aaa							2340
Glu Ile Ile Asn Leu Lys Leu Phe Glu Ile Tyr Ile Ser Thr Pro Lys							
703		708		713		718	
aat gaa ata ctt aaa tat aaa tct aac aaa tat gta caa gat cta cac							2388
Asn Glu Ile Leu Lys Tyr Lys Ser Asn Lys Tyr Val Gln Asp Leu His							
719		724		729		734	
gaa gaa cag cac aaa act ctg cag agt gag aat att ctg tat gat att							2436
Glu Glu Gln His Lys Thr Leu Gln Ser Glu Asn Ile Leu Tyr Asp Ile							
735		740		745		750	











Ile Thr Ala Ala Leu Ile Lys Gly Glu Leu Tyr Glu Arg Ala Gly Asp 802 807 812 817	
ctc ttt gag aag att cac aat cca cag aag gcc ctg gag tgc tac cgt Leu Phe Glu Lys Ile His Asn Pro Gln Lys Ala Leu Glu Cys Tyr Arg 818 823 828 833	2551
aaa ggc aac gca ttc atg aaa gcg gta gag ctg gct cga ttg gcc ttc Lys Gly Asn Ala Phe Met Lys Ala Val Glu Leu Ala Arg Leu Ala Phe 834 839 844 849	2599
cca gtg gag gtg gtg aaa cta gag gag gca tgg ggg gac cac ctg gtg Pro Val Glu Val Val Lys Leu Glu Glu Ala Trp Gly Asp His Leu Val 850 855 860 865	2647
cag cag aag cag ctt gat gca gcc att aat cac tac atc gaa gcc agg Gln Gln Lys Gln Leu Asp Ala Ala Ile Asn His Tyr Ile Glu Ala Arg 866 871 876 881	2695
tgc tcc att aag gca att gag gcc gcc ctg ggt gcc cgc cag tgg aag Cys Ser Ile Lys Ala Ile Glu Ala Ala Leu Gly Ala Arg Gln Trp Lys 882 887 892 897	2743
aag gca att tat ata tta gat cta cag gac cgg aac act gca tcc aaa Lys Ala Ile Tyr Ile Leu Asp Leu Gln Asp Arg Asn Thr Ala Ser Lys 898 903 908 913	2791
tac tat cct ctc gtg gcc caa cac tat gca tcc ctg cag gag tat gag Tyr Tyr Pro Leu Val Ala Gln His Tyr Ala Ser Leu Gln Glu Tyr Glu 914 919 924 929	2839
att gct gag gag ctc tat act aag gga gat cgg aca aaa gat gcc ata Ile Ala Glu Glu Leu Tyr Thr Lys Gly Asp Arg Thr Lys Asp Ala Ile 930 935 940 945	2887
gac atg tac acc cag gct ggt cgt tgg gaa caa gcc cac aag ctg gcg Asp Met Tyr Thr Gln Ala Gly Arg Trp Glu Gln Ala His Lys Leu Ala 946 951 956 961	2935
atg aaa tgc atg aga cca gaa gat gtg tca gtg cta tac atc act cag Met Lys Cys Met Arg Pro Glu Asp Val Ser Val Leu Tyr Ile Thr Gln 962 967 972 977	2983
gcc cag gaa atg gag aag cag ggc aag tac cgt gag gct gaa agg cta Ala Gln Glu Met Glu Lys Gln Gly Lys Tyr Arg Glu Ala Glu Arg Leu 978 983 988 993	3031
tat gtg aca gta caa gag cct gat ctt gcc atc acc atg tac aaa aag Tyr Val Thr Val Gln Glu Pro Asp Leu Ala Ile Thr Met Tyr Lys Lys 994 999 1004 1009	3079
cac aag ttg tat gat gac atg atc cgc ctg gta ggg aag cac cat cca His Lys Leu Tyr Asp Asp Met Ile Arg Leu Val Gly Lys His His Pro 1010 1015 1020 1025	3127
gat ctc ctc agt gat aca cac cta cat ctg ggc aag gag ctg gag gct Asp Leu Leu Ser Asp Thr His Leu His Leu Gly Lys Glu Leu Glu Ala 3175	

1026	1031	1036	1041	
gaa ggc cga cta cag gag gct gag tac cac tac ctc gag gcc cag gaa				3223
Glu Gly Arg Leu Gln Glu Ala Glu Tyr His Tyr Leu Glu Ala Gln Glu				
1042	1047	1052	1057	
tgg aag gca aca gtg aac atg tac cgg gcc agt ggg ctt tgg gaa gag				3271
Trp Lys Ala Thr Val Asn Met Tyr Arg Ala Ser Gly Leu Trp Glu Glu				
1058	1063	1068	1073	
gcc tac agg gtg gcc aga act caa gga ggg gct aat gcc cac aaa cac				3319
Ala Tyr Arg Val Ala Arg Thr Gln Gly Gly Ala Asn Ala His Lys His				
1074	1079	1084	1089	
gtg gcc tat ctg tgg gca aag agc ctg gga gga gag gct gca gtt aga				3367
Val Ala Tyr Leu Trp Ala Lys Ser Leu Gly Gly Glu Ala Ala Val Arg				
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ctg ctt aat aag ctg gga ctc ctg gaa gct gct gtt gac cac gct gca				3415
Leu Leu Asn Lys Leu Gly Leu Leu Glu Ala Ala Val Asp His Ala Ala				
1106	1111	1116	1121	
gac aat tgc tcc ttt gaa ttt gcg ttt gaa ctc tct cgg ctg gcc ctc				3463
Asp Asn Cys Ser Phe Glu Phe Ala Phe Glu Leu Ser Arg Leu Ala Leu				
1122	1127	1132	1137	
aag cac aaa acc ccc gag gtt cat ctc aaa tat gct atg ttc ctg gag				3511
Lys His Lys Thr Pro Glu Val His Leu Lys Tyr Ala Met Phe Leu Glu				
1138	1143	1148	1153	
gat gag ggt aaa ttc gaa gag gct gaa gct gaa ttc atc aga gct ggt				3559
Asp Glu Gly Lys Phe Glu Glu Ala Glu Ala Glu Phe Ile Arg Ala Gly				
1154	1159	1164	1169	
aaa ccc aag gag gca gtc ctc atg ttt gtc cat aac cag gat tgg gag				3607
Lys Pro Lys Glu Ala Val Leu Met Phe Val His Asn Gln Asp Trp Glu				
1170	1175	1180	1185	
gca gct cag cgt gtg gct gag gct cac gac cct gac agt gtc gcc gag				3655
Ala Ala Gln Arg Val Ala Glu Ala His Asp Pro Asp Ser Val Ala Glu				
1186	1191	1196	1201	
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Val Leu Val Gly Gln Ala Arg Gly Ala Leu Glu Glu Lys Asp Phe Gln				
1202	1207	1212	1217	
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Lys Ala Glu Gly Leu Leu Leu Arg Ala Gln Arg Pro Gly Leu Ala Leu				
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Asn Tyr Tyr Lys Glu Ala Gly Leu Trp Ser Asp Ala Leu Arg Ile Cys				
1234	1239	1244	1249	
aag gac tat gtg ccc agc cag ctg gag gct ctg cag gaa gaa tat gag				3847
Lys Asp Tyr Val Pro Ser Gln Leu Glu Ala Leu Gln Glu Glu Tyr Glu				
1250	1255	1260	1265	



cgg gaa gct act aag aag ggg gcc agg ggt gtg gag gga ttt gtg gaa	3895
Arg Glu Ala Thr Lys Lys Gly Ala Arg Gly Val Glu Gly Phe Val Glu	
1266 1271 1276 1281	
caa gct cga cac tgg gag cag gct gga gag tac agc cgt gcc gtg gac	3943
Gln Ala Arg His Trp Glu Gln Ala Gly Glu Tyr Ser Arg Ala Val Asp	
1282 1287 1292 1297	
tgc tac ctc aaa gtg cga gac tct gga aac agc ggc ctg gcg gag aag	3991
Cys Tyr Leu Lys Val Arg Asp Ser Gly Asn Ser Gly Leu Ala Glu Lys	
1298 1303 1308 1313	
tgc tgg atg aag gca gct gaa ctc tcc atc aag ttt ctg cct ccc caa	4039
Cys Trp Met Lys Ala Ala Glu Leu Ser Ile Lys Phe Leu Pro Pro Gln	
1314 1319 1324 1329	
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Arg Asn Met Glu Val Val Leu Ala Val Gly Pro Gln Leu Ile Gly Ile	
1330 1335 1340 1345	
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Gly Lys His Ser Ala Ala Ala Glu Leu Tyr Leu Asn Leu Asp Leu Val	
1346 1351 1356 1361	
aag gaa gca atc gat gct ttc atc gag ggt gag gag tgg aac aag gcg	4183
Lys Glu Ala Ile Asp Ala Phe Ile Glu Gly Glu Glu Trp Asn Lys Ala	
1362 1367 1372 1377	
aag cgt gta gct aag gag tta gat ccc agg tat gaa gac tat gtg gac	4231
Lys Arg Val Ala Lys Glu Leu Asp Pro Arg Tyr Glu Asp Tyr Val Asp	
1378 1383 1388 1393	
cag cat tat aaa gag ttc ctc aag aat cag ggc aaa gtg gac tcg ctg	4279
Gln His Tyr Lys Glu Phe Leu Lys Asn Gln Gly Lys Val Asp Ser Leu	
1394 1399 1404 1409	
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Val Gly Val Asp Val Ile Ala Ala Leu Asp Leu Tyr Val Glu Gln Gly	
1410 1415 1420 1425	
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Gln Trp Asp Lys Cys Ile Glu Thr Ala Thr Lys Gln Asn Tyr Lys Ile	
1426 1431 1436 1441	
ctg cac aag tat gtg gct ttg tat gca act cac ttg atc cgg gag ggt	4423
Leu His Lys Tyr Val Ala Leu Tyr Ala Thr His Leu Ile Arg Glu Gly	
1442 1447 1452 1457	
agc tct gcc cag gca ttg gcc ctg tat gta cag cac gga gcc cct gct	4471
Ser Ser Ala Gln Ala Leu Ala Leu Tyr Val Gln His Gly Ala Pro Ala	
1458 1463 1468 1473	
aac cca cag aac ttc aat atc tac aaa agg atc ttc act gac atg gtg	4519
Asn Pro Gln Asn Phe Asn Ile Tyr Lys Arg Ile Phe Thr Asp Met Val	
1474 1479 1484 1489	

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Ser Ser Pro Gly Thr Asn Cys Ala Glu Ala Tyr His Ser Trp Ala Asp	
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ctt cga gat gtc ctc ttc aac ctg tgt gaa aac ctg gtg aag tcc agt	4615
Leu Arg Asp Val Leu Phe Asn Leu Cys Glu Asn Leu Val Lys Ser Ser	
1506 1511 1516 1521	
gag gca aac tct cca gcc cat gag gag ttc aag acg atg ctg ctg atc	4663
Glu Ala Asn Ser Pro Ala His Glu Glu Phe Lys Thr Met Leu Leu Ile	
1522 1527 1532 1537	
gct cat tac tat gcc acg cgc tct gca gcc cag agt gtc aaa cag ctg	4711
Ala His Tyr Tyr Ala Thr Arg Ser Ala Ala Gln Ser Val Lys Gln Leu	
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Glu Thr Val Ala Ala Arg Leu Ser Val Ser Leu Leu Arg His Thr Gln	
1554 1559 1564 1569	
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Leu Leu Pro Val Asp Lys Ala Phe Tyr Glu Ala Gly Ile Ala Ala Lys	
1570 1575 1580 1585	
gca gtt ggc tgg gat aac atg gca ttc atc ttc ctc aat cgc ttt ttg	4855
Ala Val Gly Trp Asp Asn Met Ala Phe Ile Phe Leu Asn Arg Phe Leu	
1586 1591 1596 1601	
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Asp Leu Thr Asp Ala Ile Glu Glu Gly Thr Leu Asp Gly Leu Asp His	
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Ser Asp Phe Gln Asp Thr Asp Ile Pro Phe Glu Val Pro Leu Pro Ala	
1618 1623 1628 1633	
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Lys Gln His Val Pro Glu Ala Glu Arg Glu Glu Val Arg Asp Trp Val	
1634 1639 1644 1649	
ctt aca gtc tcc atg gac cag cgg ctg gag cag gtt ctg cct cgg gat	5047
Leu Thr Val Ser Met Asp Gln Arg Leu Glu Gln Val Leu Pro Arg Asp	
1650 1655 1660 1665	
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Glu Arg Gly Ala Tyr Glu Ala Ser Leu Val Ala Ala Ser Thr Gly Val	
1666 1671 1676 1681	
cga gcc ctg ccc tgc ctt att aca gga tac ccc att ctg agg aac aaa	5143
Arg Ala Leu Pro Cys Leu Ile Thr Gly Tyr Pro Ile Leu Arg Asn Lys	
1682 1687 1692 1697	
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Ile Glu Phe Lys Arg Pro Gly Lys Ala Ala Asn Lys Asp Asn Trp Asn	
1698 1703 1708 1713	
aaa ttc ctt atg gcc atc aag acc tcc cac agc cca gtg tgc cag gac	5239

Lys	Phe	Leu	Met	Ala	Ile	Lys	Thr	Ser	His	Ser	Pro	Val	Cys	Gln	Asp	
1714					1719					1724					1729	
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Val	Leu	Lys	Phe	Ile	Ser	Gln	Trp	Cys	Gly	Gly	Leu	Pro	Ser	Thr	Ser	
1730					1735					1740					1745	
ttt	tcc	ttt	cag	tag	ttg	tag	agc	tgag	gaag	ag	ttag	ggc	ctc	tcc	ctc	5342
Phe	Ser	Phe	Gln	*												
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Val	Lys	Glu	Thr	Leu	Arg	Arg	Cys	Gly	Ala	Ser	Gly	Asp	Glu	Cys	Gly	
6					11					16					21	
cgt	ctg	cag	tat	gcc	ctc	acc	tgc	ctg	cgg	aag	gtg	aca	ggc	ctg	gga	150
Arg	Leu	Gln	Tyr	Ala	Leu	Thr	Cys	Leu	Arg	Lys	Val	Thr	Gly	Leu	Gly	
22					27					32					37	
ggg	gag	cac	aag	gag	gac	tcc	agt	tgg	agt	tca	ttg	gat	gcg	cgg	cgg	198
Gly	Glu	His	Lys	Glu	Asp	Ser	Ser	Trp	Ser	Ser	Leu	Asp	Ala	Arg	Arg	
38					43					48					53	
gaa	agt	ggc	tca	ggg	cct	tcc	acg	gac	acc	ctc	tca	gca	gcc	agc	ctg	246
Glu	Ser	Gly	Ser	Gly	Pro	Ser	Thr	Asp	Thr	Leu	Ser	Ala	Ala	Ser	Leu	
54					59					64					69	
ccc	tgg	ccc	cca	ggg	agc	tcc	cag	ctg	ggc	aga	gca	ggc	aac	agc	gcc	294
Pro	Trp	Pro	Pro	Gly	Ser	Ser	Gln	Leu	Gly	Arg	Ala	Gly	Asn	Ser	Ala	
70					75					80					85	
cag	ggc	cca	cgc	tcc	atc	tcc	gtg	tca	gct	ctg	ccc	gcc	tca	gac	tcc	342
Gln	Gly	Pro	Arg	Ser	Ile	Ser	Val	Ser	Ala	Leu	Pro	Ala	Ser	Asp	Ser	
86					91					96					101	
ccc	acc	ccc	agc	ttc	agt	gag	ggc	ctc	tca	gac	acc	tgt	att	ccc	ctg	390
Pro	Thr	Pro	Ser	Phe	Ser	Glu	Gly	Leu	Ser	Asp	Thr	Cys	Ile	Pro	Leu	
102					107					112					117	

cac gcc agc ggc cgg ctg acc ccc cgt gcc ctg cac agc ttc atc acc	438
His Ala Ser Gly Arg Leu Thr Pro Arg Ala Leu His Ser Phe Ile Thr	
118 123 128 133	
ccg ccc acc aca ccc cag ctg cga cgg cac acc aag ctg aag cca cca	486
Pro Pro Thr Thr Pro Gln Leu Arg Arg His Thr Lys Leu Lys Pro Pro	
134 139 144 149	
cgg acg ccc ccc cca ccc agc cgc aag gtc ttc cag ctg ctg ccc agc	534
Arg Thr Pro Pro Pro Pro Ser Arg Lys Val Phe Gln Leu Leu Pro Ser	
150 155 160 165	
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Phe Pro Thr Leu Thr Arg Ser Lys Ser His Glu Ser Gln Leu Gly Asn	
166 171 176 181	
cgc att gat gac gtc tcc tcg atg agg ttt gat ctc tcg cat gga tcc	630
Arg Ile Asp Asp Val Ser Ser Met Arg Phe Asp Leu Ser His Gly Ser	
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Pro Gln Met Val Arg Arg Asp Ile Gly Leu Ser Val Thr His Arg Phe	
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Ser Thr Lys Ser Trp Leu Ser Gln Val Cys His Val Cys Gln Lys Ser	
214 219 224 229	
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Met Ile Phe Gly Val Lys Cys Lys His Cys Arg Leu Lys Cys His Asn	
230 235 240 245	
aaa tgt acc aaa gaa gcc cct gcc tgt aga ata tcc ttc ctg cca cta	822
Lys Cys Thr Lys Glu Ala Pro Ala Cys Arg Ile Ser Phe Leu Pro Leu	
246 251 256 261	
act cgg ctt cgg agg aca gaa tct gtc ccc tcg gac atc aac aac ccg	870
Thr Arg Leu Arg Arg Thr Glu Ser Val Pro Ser Asp Ile Asn Asn Pro	
262 267 272 277	
gtg gac aga gca gcc gaa ccc cat ttt gga acc ctc ccc aaa gca ctg	918
Val Asp Arg Ala Ala Glu Pro His Phe Gly Thr Leu Pro Lys Ala Leu	
278 283 288 293	
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Thr Lys Lys Glu His Pro Pro Ala Met Asn His Leu Asp Ser Ser Ser	
294 299 304 309	
aac cct tcc tcc acc acc tcc tcc aca ccc tcc tca ccg gcg ccc ttc	1014
Asn Pro Ser Ser Thr Thr Ser Ser Thr Pro Ser Ser Pro Ala Pro Phe	
310 315 320 325	
ccg aca tca tcc aac cca tcc agc gcc acc acg ccc ccc aac ccc tca	1062
Pro Thr Ser Ser Asn Pro Ser Ser Ala Thr Thr Pro Pro Asn Pro Ser	
326 331 336 341	



His	Ala	Lys	Gly	Ile	Val	His	Lys	Asp	Leu	Lys	Ser	Lys	Asn	Val	Phe	
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Tyr	Asp	Asn	Gly	Lys	Val	Val	Ile	Thr	Asp	Phe	Gly	Leu	Phe	Gly	Ile	
582					587					592					597	
tca	ggc	gtg	gtc	cga	gag	gga	cgg	cgt	gag	aac	cag	cta	aag	ctg	tcc	1878
Ser	Gly	Val	Val	Arg	Glu	Gly	Arg	Arg	Glu	Asn	Gln	Leu	Lys	Leu	Ser	
598					603					608					613	
cac	gac	tgg	ctg	tgc	tat	ctg	gcc	cct	gag	att	gta	cgc	gag	atg	acc	1926
His	Asp	Trp	Leu	Cys	Tyr	Leu	Ala	Pro	Glu	Ile	Val	Arg	Glu	Met	Thr	
614					619					624					629	
ccc	ggg	aag	gac	gag	gat	cag	ctg	cca	ttc	tcc	aaa	gct	gct	gat	gtc	1974
Pro	Gly	Lys	Asp	Glu	Asp	Gln	Leu	Pro	Phe	Ser	Lys	Ala	Ala	Asp	Val	
630					635					640					645	
tat	gca	ttt	ggg	act	gtt	tgg	tat	gag	ctg	caa	gca	aga	gac	tgg	ccc	2022
Tyr	Ala	Phe	Gly	Thr	Val	Trp	Tyr	Glu	Leu	Gln	Ala	Arg	Asp	Trp	Pro	
646					651					656					661	
ttg	aag	aac	cag	gct	gca	gag	gca	tcc	atc	tgg	cag	att	gga	agc	ggg	2070
Leu	Lys	Asn	Gln	Ala	Ala	Glu	Ala	Ser	Ile	Trp	Gln	Ile	Gly	Ser	Gly	
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gaa	gga	atg	aag	cgt	gtc	ctg	act	tct	gtc	agc	ttg	ggg	aag	gaa	gtc	2118
Glu	Gly	Met	Lys	Arg	Val	Leu	Thr	Ser	Val	Ser	Leu	Gly	Lys	Glu	Val	
678					683					688					693	
agt	gag	atc	ctg	tcg	gcc	tgc	tgg	gct	ttc	gac	ctg	cag	gag	aga	ccc	2166
Ser	Glu	Ile	Leu	Ser	Ala	Cys	Trp	Ala	Phe	Asp	Leu	Gln	Glu	Arg	Pro	
694					699					704					709	
agc	ttc	agc	ctg	ctg	atg	gac	atg	ctg	gag	aaa	ctt	ccc	aag	ctg	aac	2214
Ser	Phe	Ser	Leu	Leu	Met	Asp	Met	Leu	Glu	Lys	Leu	Pro	Lys	Leu	Asn	
710					715					720					725	
cgg	cgg	ctc	tcc	cac	cct	gga	cac	ttc	tgg	aag	tca	gct	gac	att	aac	2262
Arg	Arg	Leu	Ser	His	Pro	Gly	His	Phe	Trp	Lys	Ser	Ala	Asp	Ile	Asn	
726					731					736					741	
agc	agc	aaa	gtt	gta	ccc	cgg	ttt	gaa	agg	ttt	ggc	ttg	ggc	gtc	ctg	2310
Ser	Ser	Lys	Val	Val	Pro	Arg	Phe	Glu	Arg	Phe	Gly	Leu	Gly	Val	Leu	
742					747					752					757	
gag	tcc	agt	aat	cca	aag	atg	tag	ccagccatat	gggtttttcgc	tgctgatctc						2364
Glu	Ser	Ser	Asn	Pro	Lys	Met	*									
758					763											
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 Met  
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 Ala His Tyr Ile Thr Phe Leu Cys Met Val Leu Val Leu Leu Leu Gln  
 2 7 12 17  
 aat tct gtg tta gct gaa gat ggg gaa gta aga tca agt tgt cgt act 213  
 Asn Ser Val Leu Ala Glu Asp Gly Glu Val Arg Ser Ser Cys Arg Thr  
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 Ala Pro Thr Asp Leu Val Phe Ile Leu Asp Gly Ser Tyr Ser Val Gly  
 34 39 44 49  
 cca gaa aac ttt gaa ata gtg aaa aag tgg ctt gtc aat atc aca aaa 309  
 Pro Glu Asn Phe Glu Ile Val Lys Lys Trp Leu Val Asn Ile Thr Lys  
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 Asn Phe Asp Ile Gly Pro Lys Phe Ile Gln Val Gly Val Val Gln Tyr  
 66 71 76 81  
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 Ser Asp Tyr Pro Val Leu Glu Ile Pro Leu Gly Ser Tyr Asp Ser Gly  
 82 87 92 97  
 gaa cat ttg acg gca gca gtg gaa tcc ata ctc tac tta gga gga aac 453  
 Glu His Leu Thr Ala Ala Val Glu Ser Ile Leu Tyr Leu Gly Gly Asn  
 98 103 108 113  
 aca aag aca ggg aag gcc atc cag ttt gcg ctc gat tac ctt ttt gcc 501  
 Thr Lys Thr Gly Lys Ala Ile Gln Phe Ala Leu Asp Tyr Leu Phe Ala  
 114 119 124 129  
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 Lys Ser Ser Arg Phe Leu Thr Lys Ile Ala Val Val Leu Thr Asp Gly

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aag tcc caa gat gac gtc aag gat gca gct caa gca gca aga gat agt				597
Lys Ser Gln Asp Asp Val Lys Asp Ala Ala Gln Ala Ala Arg Asp Ser				
146	151	156	161	
aag ata aca tta ttt gct att ggt gtt ggt tca gaa aca gaa gat gcc				645
Lys Ile Thr Leu Phe Ala Ile Gly Val Gly Ser Glu Thr Glu Asp Ala				
162	167	172	177	
gaa ctt aga gct att gcc aac aag cct tcg tct act tat gtg ttt tat				693
Glu Leu Arg Ala Ile Ala Asn Lys Pro Ser Ser Thr Tyr Val Phe Tyr				
178	183	188	193	
gtg gaa gac tat att gca ata tcc aaa ata agg gaa gtg atg aag cag				741
Val Glu Asp Tyr Ile Ala Ile Ser Lys Ile Arg Glu Val Met Lys Gln				
194	199	204	209	
aaa ctt tgt gaa gaa tct gtc tgt cca aca cga att cca gtg gca gct				789
Lys Leu Cys Glu Glu Ser Val Cys Pro Thr Arg Ile Pro Val Ala Ala				
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cgt gat gaa agg gga ttt gat att ctt tta ggt tta gat gta aat aaa				837
Arg Asp Glu Arg Gly Phe Asp Ile Leu Leu Gly Leu Asp Val Asn Lys				
226	231	236	241	
aag gtt aag aaa aga ata cag ctt tca cca aaa aag ata aaa gga tat				885
Lys Val Lys Lys Arg Ile Gln Leu Ser Pro Lys Lys Ile Lys Gly Tyr				
242	247	252	257	
gaa gta aca tca aaa gtt gat tta tca gaa ctc aca agc aat gtt ttc				933
Glu Val Thr Ser Lys Val Asp Leu Ser Glu Leu Thr Ser Asn Val Phe				
258	263	268	273	
cca gaa ggt ctt cct cca tca tat gta ttt gtg tct act caa aga ttt				981
Pro Glu Gly Leu Pro Pro Ser Tyr Val Phe Val Ser Thr Gln Arg Phe				
274	279	284	289	
aaa gtc aag aaa att tgg gat tta tgg aga ata tta act att gat gga				1029
Lys Val Lys Lys Ile Trp Asp Leu Trp Arg Ile Leu Thr Ile Asp Gly				
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tgc cac aaa tag cag ttaccttaaa tgggtgtggac aaaatcttat tatttacaac				1084
Cys His Lys *				
306				
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1 5 10

agc atg ttt ttg aac aca tta aca ccg aag ttc tac gtg gcc cta aca 96  
Ser Met Phe Leu Asn Thr Leu Thr Pro Lys Phe Tyr Val Ala Leu Thr  
17 22 27 32

ggc act tcc tca cta ata tca ggg ctt att ttg ata ttt gaa tgg tgg 144  
Gly Thr Ser Ser Leu Ile Ser Gly Leu Ile Leu Ile Phe Glu Trp Trp  
33 38 43 48

tat ttt cgc aaa tac gga act tca ttc att gaa caa gtc tca gta agc 192  
Tyr Phe Arg Lys Tyr Gly Thr Ser Phe Ile Glu Gln Val Ser Val Ser  
49 54 59 64

cac ttg cgc ccc ctt ctg gga ggg gtt gac aac aac tct tcc aac aat 240  
His Leu Arg Pro Leu Leu Gly Gly Val Asp Asn Asn Ser Ser Asn Asn  
65 70 75 80

tct aat tcc agt aac ggg gac tca gat tcc aat agg caa agt gtc tca 288  
Ser Asn Ser Ser Asn Gly Asp Ser Asp Ser Asn Arg Gln Ser Val Ser  
81 86 91 96

gaa tgc aaa gta tgg cga aat cca cta aat tta ttt agg ggt gct gaa 336  
Glu Cys Lys Val Trp Arg Asn Pro Leu Asn Leu Phe Arg Gly Ala Glu  
97 102 107 112

tac aat cgg tat act tgg gtg aca gga cga gag cct ctt act tac tat 384  
Tyr Asn Arg Tyr Thr Trp Val Thr Gly Arg Glu Pro Leu Thr Tyr Tyr  
113 118 123 128

gac atg aat ctc tct gcc caa gac cac cag aca ttc ttt act tgt gac 432

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129					134					139					144	
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Ser	Asp	His	Leu	Arg	Pro	Ala	Asp	Ala	Ile	Met	Gln	Lys	Ala	Trp	Arg	
145					150					155					160	
gag	aga	aac	ccc	caa	gct	agg	att	tct	gca	gct	cat	gaa	gcc	ttg	gag	528
Glu	Arg	Asn	Pro	Gln	Ala	Arg	Ile	Ser	Ala	Ala	His	Glu	Ala	Leu	Glu	
161					166					171					176	
ata	aat	gag	acg	aga	cac	caa	tgt	ctt	ggc	gta	cat	caa	aag	aag	gct	576
Ile	Asn	Glu	Thr	Arg	His	Gln	Cys	Leu	Gly	Val	His	Gln	Lys	Lys	Ala	
177					182					187					192	
agc	aat	gtg	tgc	cag	aag	act	cgg	gag	gac	cag	gga	agc	aaa	gcc	ctt	624
Ser	Asn	Val	Cys	Gln	Lys	Thr	Arg	Glu	Asp	Gln	Gly	Ser	Lys	Ala	Leu	
193					198					203					208	
ctg	gaa	cta	caa	gca	tat	gct	gat	gtt	cag	gca	gtc	tta	gca	aag	tat	672
Leu	Glu	Leu	Gln	Ala	Tyr	Ala	Asp	Val	Gln	Ala	Val	Leu	Ala	Lys	Tyr	
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Asp	Asp	Ile	Ser	Leu	Pro	Lys	Ser	Ala	Thr	Ile	Cys	Tyr	Thr	Ala	Ala	
225					230					235					240	
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Leu	Leu	Lys	Ala	Arg	Ala	Val	Ser	Asp	Lys	Phe	Ser	Pro	Glu	Ala	Ala	
241					246					251					256	
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Ser	Arg	Arg	Gly	Leu	Ser	Thr	Ala	Glu	Met	Asn	Ala	Val	Glu	Ala	Ile	
257					262					267					272	
cat	aga	gct	gtg	gaa	ttc	aat	cct	cat	gtg	cca	aaa	tac	cta	cta	gaa	864
His	Arg	Ala	Val	Glu	Phe	Asn	Pro	His	Val	Pro	Lys	Tyr	Leu	Leu	Glu	
273					278					283					288	
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Ser	Glu	Ala	Ile	Ala	Tyr	Ala	Phe	Phe	His	Leu	Ala	His	Trp	Lys	Arg	
305					310					315					320	
gtg	gaa	ggg	gct	ttg	aat	ctt	ttg	cat	tgt	acg	tgg	gaa	ggc	act	ttt	1008
Val	Glu	Gly	Ala	Leu	Asn	Leu	Leu	His	Cys	Thr	Trp	Glu	Gly	Thr	Phe	
321					326					331					336	
cgg	atg	atc	cct	tat	ccc	ttg	gaa	aag	ggg	cac	cta	ttt	tat	cct	tac	1056
Arg	Met	Ile	Pro	Tyr	Pro	Leu	Glu	Lys	Gly	His	Leu	Phe	Tyr	Pro	Tyr	
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cca	atc	tgt	aca	gaa	aca	gca	gac	cga	gag	ctg	ctt	cca	tct	ttc	cat	1104
Pro	Ile	Cys	Thr	Glu	Thr	Ala	Asp	Arg	Glu	Leu	Leu	Pro	Ser	Phe	His	



His	Glu	Phe	Pro	Leu	Asn	Gly	Asn	Gln	Glu	Asn	Pro	Ser	Cys	Cys	Gly		
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Ile	Asp	Gly	Ile	Leu	Glu	Ala	Tyr	His	Arg	Ser	Leu	Arg	Thr	Val	Gln		
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ctg	tac	ggc	ccc	acc	aac	ttt	gcc	ccc	gtg	gtc	acc	cac	gtg	gcc	agg		528
Leu	Tyr	Gly	Pro	Thr	Asn	Phe	Ala	Pro	Val	Val	Thr	His	Val	Ala	Arg		
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aat	gca	gcg	gcc	gtg	cag	gat	ggc	tcc	cag	tac	tcg	gtg	ctg	ctc	atc		576
Asn	Ala	Ala	Ala	Val	Gln	Asp	Gly	Ser	Gln	Tyr	Ser	Val	Leu	Leu	Ile		
94					99					104					109		
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Ile	Thr	Asp	Gly	Val	Ile	Ser	Asp	Met	Ala	Gln	Thr	Lys	Glu	Ala	Ile		
110					115					120					125		
gtc	aac	gct	gcc	aag	ctc	ccc	atg	tcc	atc	att	atc	gtc	ggc	gtg	ggc		672
Val	Asn	Ala	Ala	Lys	Leu	Pro	Met	Ser	Ile	Ile	Ile	Val	Gly	Val	Gly		
126					131					136					141		
cag	gca	gag	ttc	gac	gcc	atg	gtg	gag	ctg	gat	ggc	gac	gac	gtg	cgg		720
Gln	Ala	Glu	Phe	Asp	Ala	Met	Val	Glu	Leu	Asp	Gly	Asp	Asp	Val	Arg		
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atc	tcc	tcc	cgg	ggg	aag	ctg	gct	gaa	cgc	gac	atc	gtc	cag	ttt	gta		768
Ile	Ser	Ser	Arg	Gly	Lys	Leu	Ala	Glu	Arg	Asp	Ile	Val	Gln	Phe	Val		
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Pro	Phe	Arg	Asp	Tyr	Val	Asp	Arg	Thr	Gly	Asn	His	Val	Leu	Ser	Met		
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Ala	Arg	Leu	Ala	Arg	Asp	Val	Leu	Ala	Glu	Ile	Pro	Asp	Gln	Leu	Val		
190					195					200					205		
tcc	tac	atg	aag	gca	cag	ggc	att	cgc	ccg	cgt	tcc	cca	ccc	gca	gca		912
Ser	Tyr	Met	Lys	Ala	Gln	Gly	Ile	Arg	Pro	Arg	Ser	Pro	Pro	Ala	Ala		
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Pro	Thr	His	Ser	Pro	Ser	Gln	Ser	Pro	Ala	Arg	Thr	Pro	Pro	Ala	Cys		
222					227					232					237		
ccc	ctg	cac	acg	cac	atc	tga	ac	ctggtctcag	caggcaggtg	gctggggcct							1013
Pro	Leu	His	Thr	His	Ile	*											
238					243												
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cctttgggac	atctgtgtgc	ctgggaggct	gccaggggggt	ggggcttctg	aagaccctc												1133
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 gtaccaagaa ggggagtgcc cgcggcaggg ttcattgaaa aaatccttag tgatattgac 180  
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 Met Met Asp Ser Pro Lys  
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 Ile Gly Asn Gly Leu Pro Val Ile Gly Pro Gly Thr Asp Ile Gly Ile  
 7 12 17 22  
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 Ser Ser Leu His Met Val Gly Tyr Leu Gly Lys Asn Phe Asp Ser Ala



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tct gtg ggt gat gct gcc tca gct gaa aca gcc tca gta act cac cct Ser Val Gly Asp Ala Ala Ser Ala Glu Thr Ala Ser Val Thr His Pro 535 540 545 550	1866
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gaa att gag aag gac gct cag tta aaa caa ttc ctt aca cca aaa act Glu Ile Glu Lys Asp Ala Gln Leu Lys Gln Phe Leu Thr Pro Lys Thr 695 700 705 710	2346
gaa caa tta aaa cca gaa cgt gtc aca tct cag gta tct aat ttg aag	2394



Glu 711	Gln	Leu	Lys	Pro	Glu 716	Arg	Val	Thr	Ser	Gln 721	Val	Ser	Asn	Leu	Lys 726	
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cag Gln 743	aat Asn	cag Gln	tct Ser	ctg Leu	aaa Lys 748	gaa Glu	aat Asn	cag Gln	aag Lys	aag Lys 753	cca Pro	ttt Phe	gtg Val	gga Gly	agt Ser 758	2490
tgg Trp 759	gtt Val	aaa Lys	ggc Gly	tta Leu	ata Ile 764	agc Ser	agg Arg	ggt Gly	gct Ala	tct Ser 769	ttt Phe	atg Met	cca Pro	ctc Leu	tgt Cys 774	2538
gtt Val 775	tca Ser	gct Ala	cat His	aat Asn	aga Arg 780	aac Asn	act Thr	ata Ile	act Thr	gat Asp 785	tta Leu	caa Gln	cct Pro	tca Ser	gtt Val 790	2586
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cct Pro 823	ccc Pro	atc Ile	agt Ser	aag Lys	cca Pro 828	cca Pro	gca Ala	ggc Gly	cct Pro	cca Pro 833	tcg Ser	tct Ser	aat Asn	ggc Gly	aca Thr 838	2730
gct Ala 839	gcc Ala	cac His	cca Pro	cat His	gct Ala 844	cat His	gct Ala	gct Ala	tca Ser	gaa Glu 849	gtt Val	ttg Leu	gaa Glu	aag Lys	tct Ser 854	2778
gga Gly 855	agc Ser	acc Thr	tca Ser	tgt Cys	gga Gly 860	gct Ala	caa Gln	ctc Leu	aac Asn	cac His 865	agt Ser	tct Ser	tat Tyr	ggg Gly	aat Asn 870	2826
ggt Gly 871	att Ile	tct Ser	tca Ser	gca Ala	aac Asn 876	cat His	gaa Glu	gac Asp	ttg Leu	gtg Val 881	gaa Glu	ggt Gly	cag Gln	att Ile	cat His 886	2874
aaa Lys 887	ctt Leu	cgt Arg	cta Leu	aaa Lys	ctt Leu 892	cgt Arg	aaa Lys	aag Lys	cta Leu	aag Lys 897	gca Ala	gaa Glu	aag Lys	aag Lys	aaa Lys 902	2922
tta Leu 903	gct Ala	gct Ala	ctt Leu	atg Met	tct Ser 908	tcc Ser	ccg Pro	caa Gln	agc Ser	aga Arg 913	aca Thr	gtt Val	cga Arg	agt Ser	gaa Glu 918	2970
aat Asn 919	cta Leu	gaa Glu	cag Gln	gtg Val	ccc Pro 924	cag Gln	gat Asp	ggg Gly	tct Ser	cca Pro 929	aat Asn	gat Asp	tgt Cys	gaa Glu	tca Ser 934	3018
ata Ile	gag Glu	gac Asp	ttg Leu	tta Leu	aat Asn	gag Glu	cta Leu	cca Pro	tat Tyr	cca Pro	att Ile	gat Asp	att Ile	gcc Ala	aat Asn	3066

935		940		945		950	
gag tct gca tgc acc act gtt cct ggt gtt tcc ctg tac agt agt caa							3114
Glu Ser Ala Cys Thr Thr Val Pro Gly Val Ser Leu Tyr Ser Ser Gln							
951		956		961		966	
act cat gaa gaa att tta gcg gaa tta ttg tct cct aca cct gtt tca							3162
Thr His Glu Glu Ile Leu Ala Glu Leu Leu Ser Pro Thr Pro Val Ser							
967		972		977		982	
aca gag ctg tca gaa aat ggg gaa ggt gac ttt agg tat ttg gga atg							3210
Thr Glu Leu Ser Glu Asn Gly Glu Gly Asp Phe Arg Tyr Leu Gly Met							
983		988		993		998	
gga gat agt cat atc cca cca cca gta cca agt gaa ttc aat gat gtt							3258
Gly Asp Ser His Ile Pro Pro Pro Val Pro Ser Glu Phe Asn Asp Val							
999		1004		1009		1014	
tcc cag aac aca cat ctg aga cag gac cat aat tat tgt agc ccc acc							3306
Ser Gln Asn Thr His Leu Arg Gln Asp His Asn Tyr Cys Ser Pro Thr							
1015		1020		1025		1030	
aag aaa aat cca tgt gaa gtt cag cca gac tct ctg aca aat aat gcc							3354
Lys Lys Asn Pro Cys Glu Val Gln Pro Asp Ser Leu Thr Asn Asn Ala							
1031		1036		1041		1046	
tgc gtt aga aca tta aac ttg gag agt ccg atg aag act gat att ttc							3402
Cys Val Arg Thr Leu Asn Leu Glu Ser Pro Met Lys Thr Asp Ile Phe							
1047		1052		1057		1062	
gat gag ttt ttt tcc tcc tca gca tta aat gct tta gca aat gac aca							3450
Asp Glu Phe Phe Ser Ser Ser Ala Leu Asn Ala Leu Ala Asn Asp Thr							
1063		1068		1073		1078	
tta gac cta cct cat ttc gat gaa tat ctg ttt gag aat tat tga att							3498
Leu Asp Leu Pro His Phe Asp Glu Tyr Leu Phe Glu Asn Tyr *							
1079		1084		1089			
aatgcttggtt aactttttttc atataatatt tattattatt agaagaactt acaatgtggtt							3558
caggtagtgt ttatacactg gacttggtgta attacttggtg taataacccat gaacaaaatg							3618
caaggtttaa cctttggttc tgcccatgaa gcatgtaatc tttcttacac attaaaatca							3678
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 <212> DNA  
 <213> Homo sapiens

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 <222> (71) .. (1792)

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              Met Asp Ala Lys Ser Leu Thr Ala Trp Ser Arg Thr Leu
                1             5             10

gtg acc ttc aag gat gta ttt gtg gac ttc acc agg gag gag tgg aag      157
Val Thr Phe Lys Asp Val Phe Val Asp Phe Thr Arg Glu Glu Trp Lys
  14             19             24             29

ctg ctg gac act gct cag cag atc gtg tac aga aat gtg atg ctg gag      205
Leu Leu Asp Thr Ala Gln Gln Ile Val Tyr Arg Asn Val Met Leu Glu
  30             35             40             45

aac tat aag aac ctg gtt tcc ttg ggt tat cag ctt act aag cca gat      253
Asn Tyr Lys Asn Leu Val Ser Leu Gly Tyr Gln Leu Thr Lys Pro Asp
  46             51             56             61

gtg atc ctc cgg ttg gag aag gga gaa gag ccc tgg ctg gtg gag aga      301
Val Ile Leu Arg Leu Glu Lys Gly Glu Glu Pro Trp Leu Val Glu Arg
  62             67             72             77

gaa att cac caa gag acc cat cct gat tca gag act gca ttt gaa atc      349
Glu Ile His Gln Glu Thr His Pro Asp Ser Glu Thr Ala Phe Glu Ile
  78             83             88             93

aaa tca tca gtt tcc agc agg agc att ttt aaa gat aag caa tcc tgt      397
Lys Ser Ser Val Ser Ser Arg Ser Ile Phe Lys Asp Lys Gln Ser Cys
  94             99             104            109

gac att aaa atg gaa gga atg gca agg aat gat ctc tgg tat ttg tca      445
Asp Ile Lys Met Glu Gly Met Ala Arg Asn Asp Leu Trp Tyr Leu Ser
 110             115            120            125

tta gaa gaa gtc tgg aaa tgt aga gac cag tta gac aag tat cag gaa      493
Leu Glu Glu Val Trp Lys Cys Arg Asp Gln Leu Asp Lys Tyr Gln Glu
 126             131            136            141

aac cca gag aga cat ttg agg caa gtg gca ttc acc caa aag aaa gta      541
Asn Pro Glu Arg His Leu Arg Gln Val Ala Phe Thr Gln Lys Lys Val
 142             147            152            157

ctt act cag gag aga gtc tct gaa agt ggt aaa tat ggg gga aac tgt      589
Leu Thr Gln Glu Arg Val Ser Glu Ser Gly Lys Tyr Gly Gly Asn Cys
 158             163            168            173

ctt ctt cct gct cag cta gta ctg aga gag tat ttc cat aaa cgt gac      637
Leu Leu Pro Ala Gln Leu Val Leu Arg Glu Tyr Phe His Lys Arg Asp
 174             179            184            189

tca cat act aaa agt tta aaa cat gat tta gtt ctt aat ggt cat cag      685
Ser His Thr Lys Ser Leu Lys His Asp Leu Val Leu Asn Gly His Gln
 190             195            200            205

gac agt tgt gca agt aac agt aat gaa tgt ggt caa act ttc tgt caa      733

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430	435	440	445	
tct cac ctt tat tca cat caa aga acc cac act gga gag aaa cca tat				1453
Ser His Leu Tyr Ser His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr				
446	451	456	461	
gag tgt cat gat tgt gga aaa tct ttc agc cag agt tct gcc ctt att				1501
Glu Cys His Asp Cys Gly Lys Ser Phe Ser Gln Ser Ser Ala Leu Ile				
462	467	472	477	
gtg cat cag agg ata cac act gga gag aaa cca tat gaa tgc tgt cag				1549
Val His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Cys Gln				
478	483	488	493	
tgt ggg aaa gcc ttc atc cgg aag aat gac ctc att aag cac cag aga				1597
Cys Gly Lys Ala Phe Ile Arg Lys Asn Asp Leu Ile Lys His Gln Arg				
494	499	504	509	
att cat gtt gga gaa gag acc tat aaa tgt aat caa tgt ggc att atc				1645
Ile His Val Gly Glu Glu Thr Tyr Lys Cys Asn Gln Cys Gly Ile Ile				
510	515	520	525	
ttc agc cag aac tct cca ttt ata gtt cat caa ata gct cac act gga				1693
Phe Ser Gln Asn Ser Pro Phe Ile Val His Gln Ile Ala His Thr Gly				
526	531	536	541	
gag cag ttc tta aca tgc aat caa tgt ggg aca gcg ctt gtt aat acc				1741
Glu Gln Phe Leu Thr Cys Asn Gln Cys Gly Thr Ala Leu Val Asn Thr				
542	547	552	557	
tct aac ctt att gga tac cag aca aat cat att aga gaa aat gct tac				1789
Ser Asn Leu Ile Gly Tyr Gln Thr Asn His Ile Arg Glu Asn Ala Tyr				
558	563	568	573	
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*				
574				

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 <212> DNA  
 <213> Homo sapiens

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 <222> (71) .. (1390)

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caaggagggc atg gat gct aag tca cta act gcc tgg tcc cgg aca ctg	109
Met Asp Ala Lys Ser Leu Thr Ala Trp Ser Arg Thr Leu	
1 5 10	

gtg acc ttc aag gat gta ttt gtg gac ttc acc agg gag gag tgg aag	157
Val Thr Phe Lys Asp Val Phe Val Asp Phe Thr Arg Glu Glu Trp Lys	
14 19 24 29	
ctg ctg gac act gct cag cag atc gtg tac aga aat gtg atg ctg gag	205
Leu Leu Asp Thr Ala Gln Gln Ile Val Tyr Arg Asn Val Met Leu Glu	
30 35 40 45	
aac tat aag aac ctg gtt tcc ttg ggt tat cag ctt act aag cca gat	253
Asn Tyr Lys Asn Leu Val Ser Leu Gly Tyr Gln Leu Thr Lys Pro Asp	
46 51 56 61	
gtg atc ctc cgg ttg gag aag gga gaa gag ccc tgg ctg gtg gag aga	301
Val Ile Leu Arg Leu Glu Lys Gly Glu Glu Pro Trp Leu Val Glu Arg	
62 67 72 77	
gaa att cac caa gag acc cat cct gat tca gag act gca ttt gaa atc	349
Glu Ile His Gln Glu Thr His Pro Asp Ser Glu Thr Ala Phe Glu Ile	
78 83 88 93	
aaa tca tca gtt tcc agc agg agc att ttt aaa gat aag caa tcc tgt	397
Lys Ser Ser Val Ser Ser Arg Ser Ile Phe Lys Asp Lys Gln Ser Cys	
94 99 104 109	
gac att aaa atg gaa gga atg gca agg aat gat ctc tgg tat ttg tca	445
Asp Ile Lys Met Glu Gly Met Ala Arg Asn Asp Leu Trp Tyr Leu Ser	
110 115 120 125	
tta gaa gaa gtc tgg aaa tgt aga gac cag tta gac aag tat cag gaa	493
Leu Glu Glu Val Trp Lys Cys Arg Asp Gln Leu Asp Lys Tyr Gln Glu	
126 131 136 141	
aac cca gag aga cat ttg agg cat cag ctt att cat act gga gaa aaa	541
Asn Pro Glu Arg His Leu Arg His Gln Leu Ile His Thr Gly Glu Lys	
142 147 152 157	
ccc tat gag tgt aaa gaa tgt gga aag tct ttc agc cgg agt tct cac	589
Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ser Phe Ser Arg Ser Ser His	
158 163 168 173	
ctc att gga cat caa aag acc cat act ggt gag gaa ccc tat gaa tgt	637
Leu Ile Gly His Gln Lys Thr His Thr Gly Glu Glu Pro Tyr Glu Cys	
174 179 184 189	
aaa gaa tgt gga aaa tcc ttc agc tgg ttc tct cac ctt gtt act cat	685
Lys Glu Cys Gly Lys Ser Phe Ser Trp Phe Ser His Leu Val Thr His	
190 195 200 205	
cag aga act cat aca gga gac aaa ctg tac aca tgt aat cag tgt ggg	733
Gln Arg Thr His Thr Gly Asp Lys Leu Tyr Thr Cys Asn Gln Cys Gly	
206 211 216 221	
aaa tct ttt gtt cat agc tct agg ctt att aga cac cag agg aca cat	781
Lys Ser Phe Val His Ser Ser Arg Leu Ile Arg His Gln Arg Thr His	
222 227 232 237	

act gga gag aaa ccc tat gaa tgt cct gaa tgt ggg aaa tct ttc aga	829
Thr Gly Glu Lys Pro Tyr Glu Cys Pro Glu Cys Gly Lys Ser Phe Arg	
238 243 248 253	
cag agc aca cat ctc att ctg cat cag aga acc cat gtg aga gtg agg	877
Gln Ser Thr His Leu Ile Leu His Gln Arg Thr His Val Arg Val Arg	
254 259 264 269	
ccc tat gaa tgc aat gaa tgt gga aag tct tac agc cag aga tct cac	925
Pro Tyr Glu Cys Asn Glu Cys Gly Lys Ser Tyr Ser Gln Arg Ser His	
270 275 280 285	
ctt gtt gtg cat cat aga att cac act gga cta aaa cct ttt gag tgt	973
Leu Val Val His His Arg Ile His Thr Gly Leu Lys Pro Phe Glu Cys	
286 291 296 301	
aag gat tgt gga aaa tgt ttt agt cga agc tct cac ctt tat tca cat	1021
Lys Asp Cys Gly Lys Cys Phe Ser Arg Ser Ser His Leu Tyr Ser His	
302 307 312 317	
caa aga acc cac act gga gag aaa cca tat gag tgt cat gat tgt gga	1069
Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Glu Cys His Asp Cys Gly	
318 323 328 333	
aaa tct ttc agc cag agt tct gcc ctt att gtg cat cag agg ata cac	1117
Lys Ser Phe Ser Gln Ser Ser Ala Leu Ile Val His Gln Arg Ile His	
334 339 344 349	
act gga gag aaa cca tat gaa tgc tgt cag tgt ggg aaa gcc ttc atc	1165
Thr Gly Glu Lys Pro Tyr Glu Cys Cys Gln Cys Gly Lys Ala Phe Ile	
350 355 360 365	
cgg aag aat gac ctc att aag cac cag aga att cat gtt gga gaa gag	1213
Arg Lys Asn Asp Leu Ile Lys His Gln Arg Ile His Val Gly Glu Glu	
366 371 376 381	
acc tat aaa tgt aat caa tgt ggc att atc ttc agc cag aac tct cca	1261
Thr Tyr Lys Cys Asn Gln Cys Gly Ile Ile Phe Ser Gln Asn Ser Pro	
382 387 392 397	
ttt ata gtt cat caa ata gct cac act gga gag cag ttc tta aca tgc	1309
Phe Ile Val His Gln Ile Ala His Thr Gly Glu Gln Phe Leu Thr Cys	
398 403 408 413	
aat caa tgt ggg aca gcg ctt gtt aat acc tct aac ctt att gga tac	1357
Asn Gln Cys Gly Thr Ala Leu Val Asn Thr Ser Asn Leu Ile Gly Tyr	
414 419 424 429	
cag aca aat cat att aga gaa aat gct tac taa taaatatg ggaatttttc	1408
Gln Thr Asn His Ile Arg Glu Asn Ala Tyr *	
430 435 440	
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 <222> (289)..(2127)

<220>  
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cttgaaatcc	cttgttgagg	gcctgcaacc	ttgtgcttcc	gactggagac	gccttttggtc	180
cctcggtgtc	tgcactggct	gctgggtcaag	gcttcagtgt	ggagtaattg	acactttcga	240
gaatatta	atcaaattag	agaagaaaac	tgatccataa	taataaaa	atg tct cga	297
					Met Ser Arg	
					1	
aaa att tca aag gag tca aaa aaa gtg aac atc tct agt tct ctg gaa	345					
Lys Ile Ser Lys Glu Ser Lys Lys Val Asn Ile Ser Ser Ser Leu Glu						
4 9 14 19						
tct gaa gat att agt tta gaa aca aca gtt cct acg gat gat att tcc	393					
Ser Glu Asp Ile Ser Leu Glu Thr Thr Val Pro Thr Asp Asp Ile Ser						
20 25 30 35						
tca tca gaa gag cga gag ggc aaa gtc aga atc acc agg cag cta att	441					
Ser Ser Glu Glu Arg Glu Gly Lys Val Arg Ile Thr Arg Gln Leu Ile						
36 41 46 51						
gaa cga aaa gaa cta ctt cat aat att cag tta cta aaa att gag cta	489					
Glu Arg Lys Glu Leu Leu His Asn Ile Gln Leu Leu Lys Ile Glu Leu						
52 57 62 67						
tcc cag aaa act atg atg atc gac aat ttg aaa gtg gat tat ctt aca	537					
Ser Gln Lys Thr Met Met Ile Asp Asn Leu Lys Val Asp Tyr Leu Thr						
68 73 78 83						
aag att gaa gaa ttg gag gag aaa ctt aat gat gca ctt cac cag aag	585					
Lys Ile Glu Glu Leu Glu Glu Lys Leu Asn Asp Ala Leu His Gln Lys						
84 89 94 99						
cag cta cta aca ttg aga tta gac aac caa ttg gct ttt caa cag aaa	633					
Gln Leu Leu Thr Leu Arg Leu Asp Asn Gln Leu Ala Phe Gln Gln Lys						
100 105 110 115						
gat gcc agc aaa tat caa gaa tta atg aaa caa gaa atg gaa acc att	681					
Asp Ala Ser Lys Tyr Gln Glu Leu Met Lys Gln Glu Met Glu Thr Ile						





gaa gag atg tat gaa aaa tat gta gca tcc aga gac cat tat aaa aca	1401
Glu Glu Met Tyr Glu Lys Tyr Val Ala Ser Arg Asp His Tyr Lys Thr	
356 361 366 371	
gaa tat gaa aat aaa cta cat gat gaa cta gaa caa atc aga ttg aaa	1449
Glu Tyr Glu Asn Lys Leu His Asp Glu Leu Glu Gln Ile Arg Leu Lys	
372 377 382 387	
acc aac caa gaa att gat caa ctt cga aat gcc tct agg gaa atg tat	1497
Thr Asn Gln Glu Ile Asp Gln Leu Arg Asn Ala Ser Arg Glu Met Tyr	
388 393 398 403	
gaa cga gaa aac aga aat ctc cga gaa gca agg gat aat gct gtg gct	1545
Glu Arg Glu Asn Arg Asn Leu Arg Glu Ala Arg Asp Asn Ala Val Ala	
404 409 414 419	
gaa aag gaa cga gca gtg atg gct gaa aag gat gct tta gaa aaa cac	1593
Glu Lys Glu Arg Ala Val Met Ala Glu Lys Asp Ala Leu Glu Lys His	
420 425 430 435	
gat cag ctc tta gac agg tac aga gaa cta caa ctt agt aca gaa agc	1641
Asp Gln Leu Leu Asp Arg Tyr Arg Glu Leu Gln Leu Ser Thr Glu Ser	
436 441 446 451	
aaa gta aca gaa ttt ctc cat caa agt aaa tta aaa tct ttt gaa agt	1689
Lys Val Thr Glu Phe Leu His Gln Ser Lys Leu Lys Ser Phe Glu Ser	
452 457 462 467	
gag cgt gtt caa ctt ctg caa gag gaa aca gca aga aat ctc aca cag	1737
Glu Arg Val Gln Leu Leu Gln Glu Glu Thr Ala Arg Asn Leu Thr Gln	
468 473 478 483	
tgt caa ttg gaa tgt gaa aaa tat cag aaa aaa ttg gag gtt tta acc	1785
Cys Gln Leu Glu Cys Glu Lys Tyr Gln Lys Lys Leu Glu Val Leu Thr	
484 489 494 499	
aaa gaa ttt tat agt ctc caa gcc tct tct gaa aaa cgc att act gaa	1833
Lys Glu Phe Tyr Ser Leu Gln Ala Ser Ser Glu Lys Arg Ile Thr Glu	
500 505 510 515	
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Leu Gln Ala Gln Asn Ser Glu His Gln Ala Arg Leu Asp Ile Tyr Glu	
516 521 526 531	
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Lys Leu Glu Lys Glu Leu Asp Glu Ile Ile Met Gln Thr Ala Glu Ile	
532 537 542 547	
gaa aat gaa gat gag gct gaa agg gtt ctt ttt tcc tac ggc tat ggt	1977
Glu Asn Glu Asp Glu Ala Glu Arg Val Leu Phe Ser Tyr Gly Tyr Gly	
548 553 558 563	
gct aat gtt ccc aca aca gcc aaa aga cga cta aag caa agt gtt cac	2025
Ala Asn Val Pro Thr Thr Ala Lys Arg Arg Leu Lys Gln Ser Val His	
564 569 574 579	





Arg	Leu	Met	Tyr	Asn	Ser	Ser	Asn	Pro	Val	Leu	Lys	Asn	Met	Trp	Pro	
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Glu	Gly	Lys	Leu	Ser	Ile	Thr	Glu	Val	Thr	Lys	Arg	Pro	Leu	Thr	Ala	
296					301					306					311	
gct	acc	ttg	ttt	aag	aat	tct	atg	att	gct	cta	gta	gac	aac	ctt	gca	1073
Ala	Thr	Leu	Phe	Lys	Asn	Ser	Met	Ile	Ala	Leu	Val	Asp	Asn	Leu	Ala	
312					317					322					327	
tca	aag	gaa	cca	tat	tac	gtt	cgt	tgc	atc	aaa	ccc	aat	gac	aag	aaa	1121
Ser	Lys	Glu	Pro	Tyr	Tyr	Val	Arg	Cys	Ile	Lys	Pro	Asn	Asp	Lys	Lys	
328					333					338					343	
tct	cca	cag	ata	ttt	gat	gat	gaa	cgc	tgc	cgg	cac	caa	gta	gaa	tat	1169
Ser	Pro	Gln	Ile	Phe	Asp	Asp	Glu	Arg	Cys	Arg	His	Gln	Val	Glu	Tyr	
344					349					354					359	
ctt	gga	cta	ctg	gaa	aat	gtg	aga	gtg	cgt	cgg	gca	gga	ttt	gcc	ttc	1217
Leu	Gly	Leu	Leu	Glu	Asn	Val	Arg	Val	Arg	Arg	Ala	Gly	Phe	Ala	Phe	
360					365					370					375	
cgc	cag	aca	tac	gag	aag	ttt	ctt	cac	agg	tat	aag	atg	atc	tct	gaa	1265
Arg	Gln	Thr	Tyr	Glu	Lys	Phe	Leu	His	Arg	Tyr	Lys	Met	Ile	Ser	Glu	
376					381					386					391	
ttc	acc	tgg	ccc	aac	cat	gac	ctt	cct	tca	gac	aaa	gag	gct	gtc	aag	1313
Phe	Thr	Trp	Pro	Asn	His	Asp	Leu	Pro	Ser	Asp	Lys	Glu	Ala	Val	Lys	
392					397					402					407	
aaa	cta	att	gaa	cgg	tgt	ggc	ttt	cag	gat	gat	gta	gct	tat	ggg	aag	1361
Lys	Leu	Ile	Glu	Arg	Cys	Gly	Phe	Gln	Asp	Asp	Val	Ala	Tyr	Gly	Lys	
408					413					418					423	
acc	aaa	att	ttc	att	cga	aca	ccc	cga	aca	ttg	ttt	acc	ttg	gaa	gaa	1409
Thr	Lys	Ile	Phe	Ile	Arg	Thr	Pro	Arg	Thr	Leu	Phe	Thr	Leu	Glu	Glu	
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ctc	cgt	gcc	cag	atg	ctc	ata	agg	att	gtc	ctc	ttt	cta	caa	aag	gtg	1457
Leu	Arg	Ala	Gln	Met	Leu	Ile	Arg	Ile	Val	Leu	Phe	Leu	Gln	Lys	Val	
440					445					450					455	
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Trp	Arg	Gly	Thr	Leu	Ala	Arg	Met	Arg	Tyr	Lys	Arg	Thr	Lys	Ala	Ala	
456					461					466					471	
ctg	aca	ata	atc	agg	tac	tac	cgg	cgc	tac	aaa	gtg	aag	tcg	tac	atc	1553
Leu	Thr	Ile	Ile	Arg	Tyr	Tyr	Arg	Arg	Tyr	Lys	Val	Lys	Ser	Tyr	Ile	
472					477					482					487	
cac	gag	gtg	gcc	aga	cgc	ttc	cat	ggc	gtc	aag	acc	atg	cga	gac	tac	1601
His	Glu	Val	Ala	Arg	Arg	Phe	His	Gly	Val	Lys	Thr	Met	Arg	Asp	Tyr	
488					493					498					503	
ggg	aag	cac	gtg	aag	tgg	cca	agc	cct	cct	aaa	gtt	ctt	cgc	cgt	ttt	1649
Gly	Lys	His	Val	Lys	Trp	Pro	Ser	Pro	Pro	Lys	Val	Leu	Arg	Arg	Phe	

504		509		514		519	
gag gag gcc ctg cag acg att ttc aat aga tgg aga gca tcc cag ctc							1697
Glu Glu Ala Leu Gln Thr Ile Phe Asn Arg Trp Arg Ala Ser Gln Leu							
520		525		530		535	
atc aag agc att ccg gcc tca gac ctg ccc cag gtc agg gca aag gtt							1745
Ile Lys Ser Ile Pro Ala Ser Asp Leu Pro Gln Val Arg Ala Lys Val							
536		541		546		551	
gca gcc gtg gaa atg ttg aag ggt caa agg gct gac ctc ggg ctc cag							1793
Ala Ala Val Glu Met Leu Lys Gly Gln Arg Ala Asp Leu Gly Leu Gln							
552		557		562		567	
agg gcc tgg gag ggc aac tat ctt gct tca aag cca gat aca cct cag							1841
Arg Ala Trp Glu Gly Asn Tyr Leu Ala Ser Lys Pro Asp Thr Pro Gln							
568		573		578		583	
acc tca ggc act ttt gtc cct gtt gct aat gaa ttg aaa cgg aag gac							1889
Thr Ser Gly Thr Phe Val Pro Val Ala Asn Glu Leu Lys Arg Lys Asp							
584		589		594		599	
aaa tac atg aat gtc ctc ttt tcc tgt cac gtc cgt aag gta aat cga							1937
Lys Tyr Met Asn Val Leu Phe Ser Cys His Val Arg Lys Val Asn Arg							
600		605		610		615	
ttt agt aag gtg gaa gac aga gca att ttt gtc act gac cgt cac ctg							1985
Phe Ser Lys Val Glu Asp Arg Ala Ile Phe Val Thr Asp Arg His Leu							
616		621		626		631	
tat aaa atg gat ccc act aaa cag tac aag gtg atg aag act atc cct							2033
Tyr Lys Met Asp Pro Thr Lys Gln Tyr Lys Val Met Lys Thr Ile Pro							
632		637		642		647	
cta tac aat ttg act ggt ctg agt gtc tcc aat gga aag gac caa ctt							2081
Leu Tyr Asn Leu Thr Gly Leu Ser Val Ser Asn Gly Lys Asp Gln Leu							
648		653		658		663	
gta gtg ttc cat acg aaa gac aac aaa gac ctc att gtc tgc ctc ttc							2129
Val Val Phe His Thr Lys Asp Asn Lys Asp Leu Ile Val Cys Leu Phe							
664		669		674		679	
agc aaa cag cca acc cat gag agt cga att gga gaa ctt gtt gga gtg							2177
Ser Lys Gln Pro Thr His Glu Ser Arg Ile Gly Glu Leu Val Gly Val							
680		685		690		695	
ctg gtg aat cat ttc aag agt gag aag cgc cac ctt caa gtg aac gtc							2225
Leu Val Asn His Phe Lys Ser Glu Lys Arg His Leu Gln Val Asn Val							
696		701		706		711	
acc aac cca gta cag tgc agc ctg cac ggg aag aag tgc acc gtc tcc							2273
Thr Asn Pro Val Gln Cys Ser Leu His Gly Lys Lys Cys Thr Val Ser							
712		717		722		727	
gtg gag acg cgg ctc aac cag ccc cag ccc gac ttc acc aag aat cgc							2321
Val Glu Thr Arg Leu Asn Gln Pro Gln Pro Asp Phe Thr Lys Asn Arg							
728		733		738		743	



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aggcagaggt gccctcagcc cagattagca acactcatag ttttgccaat taccagtaga 3992
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                        1              5

att cag cga tat ctg gtt tat gcc ata ctc tgg tcc ctg tct gga gac 159
Ile Gln Arg Tyr Leu Val Tyr Ala Ile Leu Trp Ser Leu Ser Gly Asp
10              15              20              25

agc cgg cta aaa atg aga gca gag ctg ggt gaa tac atc aga aga atc 207
Ser Arg Leu Lys Met Arg Ala Glu Leu Gly Glu Tyr Ile Arg Arg Ile
26              31              36              41

acg acc gtg cct ctg ccc act gcg ccc aac ata ccc att atc gat tat 255
Thr Thr Val Pro Leu Pro Thr Ala Pro Asn Ile Pro Ile Ile Asp Tyr
42              47              52              57

gag gtg tcc atc agc gga gaa tgg tct ccg tgg cag gcc aag gtg cct 303
Glu Val Ser Ile Ser Gly Glu Trp Ser Pro Trp Gln Ala Lys Val Pro
58              63              68              73

cag att gaa gtg gag acg cac aag gtg gca gcc cct gat gtc gtc gtg 351
Gln Ile Glu Val Glu Thr His Lys Val Ala Ala Pro Asp Val Val Val

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tat tca ccc cgt gaa atg act agg tgg gtg aga ggc atc ttt gaa gcg	1071
Tyr Ser Pro Arg Glu Met Thr Arg Trp Val Arg Gly Ile Phe Glu Ala	
314 319 324 329	
ctg aga cct ctg gag acc ctg cct gtt gaa ggc ctc att cgg att tgg	1119
Leu Arg Pro Leu Glu Thr Leu Pro Val Glu Gly Leu Ile Arg Ile Trp	
330 335 340 345	
gca cat gaa gct ctg cgt ctc ttc caa gat aga ctc gta gag gat gag	1167
Ala His Glu Ala Leu Arg Leu Phe Gln Asp Arg Leu Val Glu Asp Glu	
346 351 356 361	
gag agg cgt tgg act gat gag aac atc gac acg gtt gct ctg aag cac	1215
Glu Arg Arg Trp Thr Asp Glu Asn Ile Asp Thr Val Ala Leu Lys His	
362 367 372 377	
ttc cct aac atc gac aga gag aag gca atg agc cga ccc atc ttg tac	1263
Phe Pro Asn Ile Asp Arg Glu Lys Ala Met Ser Arg Pro Ile Leu Tyr	
378 383 388 393	
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Ser Asn Trp Leu Ser Lys Asp Tyr Ile Pro Val Asp Gln Glu Glu Leu	
394 399 404 409	
aga gat tat gtc aaa gct agg ctg aag gtc ttt tat gaa gaa gaa ctt	1359
Arg Asp Tyr Val Lys Ala Arg Leu Lys Val Phe Tyr Glu Glu Glu Leu	
410 415 420 425	
gat gtt ccg ctg gtg ctg ttt aat gaa gtc cta gac cac gtg ctg agg	1407
Asp Val Pro Leu Val Leu Phe Asn Glu Val Leu Asp His Val Leu Arg	
426 431 436 441	
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Ile Asp Arg Ile Phe Arg Gln Pro Gln Gly His Leu Leu Leu Ile Gly	
442 447 452 457	
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Val Ser Gly Ala Gly Lys Thr Thr Leu Ser Arg Phe Val Ala Trp Met	
458 463 468 473	
aac ggt ttg agt gtg tac cag att aag gtc cat agg aag tac aca ggg	1551
Asn Gly Leu Ser Val Tyr Gln Ile Lys Val His Arg Lys Tyr Thr Gly	
474 479 484 489	
gaa gac ttt gat gaa gat cta cgg aca gtg ttg aga cgt tct ggc tgt	1599
Glu Asp Phe Asp Glu Asp Leu Arg Thr Val Leu Arg Arg Ser Gly Cys	
490 495 500 505	
aaa aat gaa aag ata gca ttt ata atg gat gaa tct aat gtg tta gat	1647
Lys Asn Glu Lys Ile Ala Phe Ile Met Asp Glu Ser Asn Val Leu Asp	
506 511 516 521	
tct gga ttc ctg gag cga atg aat acc ctt ctg gcc aat gga gag gtg	1695
Ser Gly Phe Leu Glu Arg Met Asn Thr Leu Leu Ala Asn Gly Glu Val	
522 527 532 537	



Lys Met Val Lys Asp Gln Gln Glu Ala Glu Lys Lys Lys Val Met Ser	
762 767 772 777	
caa gaa atc cag gaa cag ctg cat aag cag cag gag gta att gca gac	2463
Gln Glu Ile Gln Glu Gln Leu His Lys Gln Gln Glu Val Ile Ala Asp	
778 783 788 793	
aaa cag atg agt gtc aaa gaa gat ctt gat aag gtg gaa cct gcc gtc	2511
Lys Gln Met Ser Val Lys Glu Asp Leu Asp Lys Val Glu Pro Ala Val	
794 799 804 809	
att gag gcc cag aat gct gtg aag tcg atc aag aag cag cac ctg gtg	2559
Ile Glu Ala Gln Asn Ala Val Lys Ser Ile Lys Lys Gln His Leu Val	
810 815 820 825	
gag gtg agg tcc atg gcc aac cct cct gct gct gtg aag ctg gcg ctg	2607
Glu Val Arg Ser Met Ala Asn Pro Pro Ala Ala Val Lys Leu Ala Leu	
826 831 836 841	
gag tcc atc tgc ctg ctg ctg ggg gaa agc acc aca gac tgg aag cag	2655
Glu Ser Ile Cys Leu Leu Leu Gly Glu Ser Thr Thr Asp Trp Lys Gln	
842 847 852 857	
atc cgc tcc atc atc atg cgg gag aac ttc atc ccc acc atc gtc aac	2703
Ile Arg Ser Ile Ile Met Arg Glu Asn Phe Ile Pro Thr Ile Val Asn	
858 863 868 873	
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Phe Ser Ala Glu Glu Ile Ser Asp Ala Ile Arg Glu Lys Met Lys Lys	
874 879 884 889	
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Asn Tyr Met Ser Asn Pro Ser Tyr Asn Tyr Glu Ile Val Asn Arg Ala	
890 895 900 905	
tcc ctg gct tgc ggc cct atg gtg aaa tgg gca att gca cag ctt aac	2847
Ser Leu Ala Cys Gly Pro Met Val Lys Trp Ala Ile Ala Gln Leu Asn	
906 911 916 921	
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Tyr Ala Asp Met Leu Lys Arg Val Glu Pro Leu Arg Asn Glu Leu Gln	
922 927 932 937	
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Lys Leu Glu Asp Asp Ala Lys Asp Asn Gln Gln Lys Ala Asn Glu Val	
938 943 948 953	
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Glu Gln Met Ile Arg Asp Leu Glu Ala Ser Ile Ala Arg Tyr Lys Glu	
954 959 964 969	
gaa tac gcc gtc ctg atc tca gag gcc cag gcc atc aag gca gac ctg	3039
Glu Tyr Ala Val Leu Ile Ser Glu Ala Gln Ala Ile Lys Ala Asp Leu	
970 975 980 985	
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Ala Ala Val Glu Ala Lys Val Asn Arg Ser Thr Ala Leu Leu Lys Ser	

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Leu Ser Ala Glu Arg Glu Arg Trp Glu Lys Thr Ser Glu Thr Phe Lys				
1002	1007	1012	1017	
aac cag atg tcc acc att gct ggg gac tgt ctc ttg tca gct gcg ttc				3183
Asn Gln Met Ser Thr Ile Ala Gly Asp Cys Leu Leu Ser Ala Ala Phe				
1018	1023	1028	1033	
att gcc tac gcg ggt tac ttt gac cag cag atg cgt cag aac ttg ttc				3231
Ile Ala Tyr Ala Gly Tyr Phe Asp Gln Gln Met Arg Gln Asn Leu Phe				
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act acc tgg tcc cat cac cta cag caa gcc aac atc cag ttc cgt aca				3279
Thr Thr Trp Ser His His Leu Gln Gln Ala Asn Ile Gln Phe Arg Thr				
1050	1055	1060	1065	
gat att gcc agg acg gaa tac ctt tcc aat gct gat gag cgt ctt cgc				3327
Asp Ile Ala Arg Thr Glu Tyr Leu Ser Asn Ala Asp Glu Arg Leu Arg				
1066	1071	1076	1081	
tgg cag gcc agc tcc ttg cct gct gat gac ctt tgc aca gaa aat gcc				3375
Trp Gln Ala Ser Ser Leu Pro Ala Asp Asp Leu Cys Thr Glu Asn Ala				
1082	1087	1092	1097	
atc atg ctg aaa cga ttc aat agg tat ccg ctg atc att gac ccc tct				3423
Ile Met Leu Lys Arg Phe Asn Arg Tyr Pro Leu Ile Ile Asp Pro Ser				
1098	1103	1108	1113	
gga cag gcc aca gaa ttc att atg aat gaa tat aag gat cgt aag atc				3471
Gly Gln Ala Thr Glu Phe Ile Met Asn Glu Tyr Lys Asp Arg Lys Ile				
1114	1119	1124	1129	
aca cgg acc agc ttc ctg gat gac gcc ttc aga aag aac tta gag agt				3519
Thr Arg Thr Ser Phe Leu Asp Asp Ala Phe Arg Lys Asn Leu Glu Ser				
1130	1135	1140	1145	
gca ctg aga ttc ggt aac ccc ctt ctg gtc cag gat gtg gaa agc tac				3567
Ala Leu Arg Phe Gly Asn Pro Leu Leu Val Gln Asp Val Glu Ser Tyr				
1146	1151	1156	1161	
gat cca gtt ttg aac ccg gtg ctg aac cgt gaa gtg cgg cga aca ggg				3615
Asp Pro Val Leu Asn Pro Val Leu Asn Arg Glu Val Arg Arg Thr Gly				
1162	1167	1172	1177	
ggg aga gtg ctg atc act ctc ggg gac cag gac ata gac ctg tcg cca				3663
Gly Arg Val Leu Ile Thr Leu Gly Asp Gln Asp Ile Asp Leu Ser Pro				
1178	1183	1188	1193	
tcg ttt gtc atc ttc ctg tcc acc cgg gat cca act gtc gag ttc cca				3711
Ser Phe Val Ile Phe Leu Ser Thr Arg Asp Pro Thr Val Glu Phe Pro				
1194	1199	1204	1209	
cca gat ctc tgt tcc cgg gtt act ttt gta aac ttc aca gtt acc cgt				3759
Pro Asp Leu Cys Ser Arg Val Thr Phe Val Asn Phe Thr Val Thr Arg				
1210	1215	1220	1225	

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Ser Ser Leu Gln Ser Gln Cys Leu Asn Glu Val Leu Lys Ala Glu Arg	
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cct gat gtg gac gag aaa cga tct gat ctt ctt aaa ctt caa ggg gaa	3855
Pro Asp Val Asp Glu Lys Arg Ser Asp Leu Leu Lys Leu Gln Gly Glu	
1242 1247 1252 1257	
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Phe Gln Leu Arg Leu Arg Gln Leu Glu Lys Ser Leu Leu Gln Ala Leu	
1258 1263 1268 1273	
aac gag gtg aaa ggg cgc att ttg gat gac gac acg atc ata acc act	3951
Asn Glu Val Lys Gly Arg Ile Leu Asp Asp Asp Thr Ile Ile Thr Thr	
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ctg gag aac ctg aag aga gag gct gca gag gtc acc agg aaa gtt gag	3999
Leu Glu Asn Leu Lys Arg Glu Ala Ala Glu Val Thr Arg Lys Val Glu	
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Glu Thr Asp Ile Val Met Gln Glu Val Glu Thr Val Ser Gln Gln Tyr	
1306 1311 1316 1321	
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Leu Pro Leu Ser Thr Ala Cys Ser Ser Ile Tyr Phe Thr Met Glu Ser	
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Leu Lys Gln Ile His Phe Leu Tyr Gln Tyr Ser Leu Gln Phe Phe Leu	
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gac att tat cac aac gtc cta tac gag aac ccg aac ctg aag ggt gtc	4191
Asp Ile Tyr His Asn Val Leu Tyr Glu Asn Pro Asn Leu Lys Gly Val	
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Val Ala Phe Asn Arg Val Ala Arg Gly Met Leu His Gln Asp His Ile	
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acc ttt gcc atg ctg ctg gca aga atc aaa ctg aag ggc acc gtg ggg	4335
Thr Phe Ala Met Leu Leu Ala Arg Ile Lys Leu Lys Gly Thr Val Gly	
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Glu Pro Thr Tyr Asp Ala Glu Phe Gln His Phe Leu Arg Gly Asn Glu	
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Ile Val Leu Ser Ala Gly Ser Thr Pro Arg Ile Gln Gly Leu Thr Val	
1434 1439 1444 1449	







1898	1903	1908	1913	
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Thr Leu Ser His Leu Lys Arg Thr Val Glu Asn Ile Lys Asp Pro Leu				
1914	1919	1924	1929	
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Phe Arg Phe Phe Glu Arg Glu Val Lys Met Gly Ala Lys Leu Leu Gln				
1930	1935	1940	1945	
gac gtt cgc cag gac ctt gca gat gtc gtc cag gtg tgc gaa gga aag				5967
Asp Val Arg Gln Asp Leu Ala Asp Val Val Gln Val Cys Glu Gly Lys				
1946	1951	1956	1961	
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Lys Lys Gln Thr Asn Tyr Leu Arg Thr Leu Ile Asn Glu Leu Val Lys				
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ggg atc ttg cct cgg agc tgg tcc cac tac acg gtg cct gcc ggc atg				6063
Gly Ile Leu Pro Arg Ser Trp Ser His Tyr Thr Val Pro Ala Gly Met				
1978	1983	1988	1993	
acc gtc atc cag tgg gtg tcc gac ttc agc gag agg atc aaa cag ctg				6111
Thr Val Ile Gln Trp Val Ser Asp Phe Ser Glu Arg Ile Lys Gln Leu				
1994	1999	2004	2009	
cag aac atc tca ctg gca gct gca tct ggt ggc gcc aag gag cta aag				6159
Gln Asn Ile Ser Leu Ala Ala Ala Ser Gly Gly Ala Lys Glu Leu Lys				
2010	2015	2020	2025	
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Asn Ile His Val Cys Leu Gly Gly Leu Phe Val Pro Glu Ala Tyr Ile				
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act gcc acc agg cag tat gtg gcc cag gcc aac agc tgg tcc ctg gag				6255
Thr Ala Thr Arg Gln Tyr Val Ala Gln Ala Asn Ser Trp Ser Leu Glu				
2042	2047	2052	2057	
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Glu Leu Cys Leu Glu Val Asn Val Thr Thr Ser Gln Gly Ala Thr Leu				
2058	2063	2068	2073	
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Asp Ala Cys Ser Phe Gly Val Thr Gly Leu Lys Leu Gln Gly Ala Thr				
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Cys Asn Asn Asn Lys Leu Ser Leu Ser Asn Ala Ile Ser Thr Ala Leu				
2090	2095	2100	2105	
ccc ctg acg cag ctg cgc tgg gtc aag cag aca aac acc gag aag aag				6447
Pro Leu Thr Gln Leu Arg Trp Val Lys Gln Thr Asn Thr Glu Lys Lys				
2106	2111	2116	2121	
gcc agt gtg gta acc tta cct gtc tac ctg aac ttc acc cgt gca gac				6495
Ala Ser Val Val Thr Leu Pro Val Tyr Leu Asn Phe Thr Arg Ala Asp				
2122	2127	2132	2137	

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2138                2143                2148                2153

agc ttc tac gag cgg ggt gtc gca gtc ttg tgc aca gag taa acttttc      6592
Ser Phe Tyr Glu Arg Gly Val Ala Val Leu Cys Thr Glu  *
2154                2159                2164

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ggaatctgac ggttgggagt ggtggaaatt ggaaggatac caggaggtat ttgggaaggc      6772

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cgc atc ggg ccc atg aga ctg acg cag gac cct att cag gtt ttg ctg      281
Arg Ile Gly Pro Met Arg Leu Thr Gln Asp Pro Ile Gln Val Leu Leu
  9                14                19                24

atc ttt gca aag gaa gat agt cag agc gat ggc ttc tgg tgg gcc tgc      329
Ile Phe Ala Lys Glu Asp Ser Gln Ser Asp Gly Phe Trp Trp Ala Cys
 25                30                35                40

gac aga gct ggt tat aga tgc aat att gct cgg act cca gag tca gcc      377
Asp Arg Ala Gly Tyr Arg Cys Asn Ile Ala Arg Thr Pro Glu Ser Ala
 41                46                51                56

ctt gaa tgc ttt ctt gat aag cat cat gaa att att gta att gat cat      425
Leu Glu Cys Phe Leu Asp Lys His His Glu Ile Ile Val Ile Asp His
 57                62                67                72

aga caa act cag aac ttc gat gca gaa gca gtg tgc agg tcg atc cgg      473

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Ala	Thr	Asn	Pro	Ser	Glu	His	Thr	Val	Ile	Leu	Ala	Val	Val	Ser	Arg	
89					94					99					104	
gta	tcg	gat	gac	cat	gaa	gag	gcg	tca	gtc	ctt	cct	ctt	ctc	cac	gca	569
Val	Ser	Asp	Asp	His	Glu	Glu	Ala	Ser	Val	Leu	Pro	Leu	Leu	His	Ala	
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Gly	Phe	Asn	Arg	Arg	Phe	Met	Glu	Asn	Ser	Ser	Ile	Ile	Ala	Cys	Tyr	
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aat	gaa	ctg	att	caa	ata	gaa	cat	ggg	gaa	gtt	cgc	tcc	cag	ttc	aaa	665
Asn	Glu	Leu	Ile	Gln	Ile	Glu	His	Gly	Glu	Val	Arg	Ser	Gln	Phe	Lys	
137					142					147					152	
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Leu	Arg	Ala	Cys	Asn	Ser	Val	Phe	Thr	Ala	Leu	Asp	His	Cys	His	Glu	
153					158					163					168	
gcc	ata	gaa	ata	aca	agc	gat	gac	cac	gtg	att	cag	tat	gtc	aac	cca	761
Ala	Ile	Glu	Ile	Thr	Ser	Asp	Asp	His	Val	Ile	Gln	Tyr	Val	Asn	Pro	
169					174					179					184	
gcc	ttc	gaa	agg	atg	atg	ggc	tac	cac	aaa	ggg	gag	ctc	ctg	gga	aaa	809
Ala	Phe	Glu	Arg	Met	Met	Gly	Tyr	His	Lys	Gly	Glu	Leu	Leu	Gly	Lys	
185					190					195					200	
gaa	ctc	gct	gat	ctg	ccc	aaa	agc	gat	aag	aac	cgg	gca	gac	ctt	ctc	857
Glu	Leu	Ala	Asp	Leu	Pro	Lys	Ser	Asp	Lys	Asn	Arg	Ala	Asp	Leu	Leu	
201					206					211					216	
gac	acc	atc	aat	aca	tgc	atc	aag	aag	gga	aag	gag	tgg	cag	ggg	gtt	905
Asp	Thr	Ile	Asn	Thr	Cys	Ile	Lys	Lys	Gly	Lys	Glu	Trp	Gln	Gly	Val	
217					222					227					232	
tac	tat	gcc	aga	cgg	aaa	tcc	ggg	gac	agc	atc	caa	cag	cac	gtg	aag	953
Tyr	Tyr	Ala	Arg	Arg	Lys	Ser	Gly	Asp	Ser	Ile	Gln	Gln	His	Val	Lys	
233					238					243					248	
atc	acc	cca	gtg	att	ggc	caa	gga	ggg	aaa	att	agg	cat	ttt	gtc	tcg	1001
Ile	Thr	Pro	Val	Ile	Gly	Gln	Gly	Gly	Lys	Ile	Arg	His	Phe	Val	Ser	
249					254					259					264	
ctc	aag	aaa	ctg	tgt	tgt	acc	act	gac	aat	aat	aag	cag	att	cac	aag	1049
Leu	Lys	Lys	Leu	Cys	Cys	Thr	Thr	Asp	Asn	Asn	Lys	Gln	Ile	His	Lys	
265					270					275					280	
att	cat	cgt	gat	tca	gga	gac	aat	tct	cag	aca	gag	cct	cat	tca	ttc	1097
Ile	His	Arg	Asp	Ser	Gly	Asp	Asn	Ser	Gln	Thr	Glu	Pro	His	Ser	Phe	
281					286					291					296	
aga	tat	aag	aac	agg	agg	aaa	gag	tcc	att	gac	gtg	aaa	tcg	ata	tca	1145
Arg	Tyr	Lys	Asn	Arg	Arg	Lys	Glu	Ser	Ile	Asp	Val	Lys	Ser	Ile	Ser	

297		302		307		312	
tct cga ggc agt gat gca cca agc ctg cag aat cgt cgc tat ccg tcc							1193
Ser Arg Gly Ser Asp Ala Pro Ser Leu Gln Asn Arg Arg Tyr Pro Ser							
313		318		323		328	
atg gcg agg atc cac tcc atg acc atc gag gct ccc atc aca aag gtt							1241
Met Ala Arg Ile His Ser Met Thr Ile Glu Ala Pro Ile Thr Lys Val							
329		334		339		344	
ata aat ata atc aat gca gcc caa gaa aac agc cca gtc aca gta gcg							1289
Ile Asn Ile Ile Asn Ala Ala Gln Glu Asn Ser Pro Val Thr Val Ala							
345		350		355		360	
gaa gcc ttg gac aga gtt cta gag att tta cgg acc aca gaa ctg tac							1337
Glu Ala Leu Asp Arg Val Leu Glu Ile Leu Arg Thr Thr Glu Leu Tyr							
361		366		371		376	
tcc cct cag ctg ggt acc aaa gat gaa gat ccc cac acc agt gat ctt							1385
Ser Pro Gln Leu Gly Thr Lys Asp Glu Asp Pro His Thr Ser Asp Leu							
377		382		387		392	
gtt gga ggc ctg atg act gac ggc ttg aga aga ctg tca gga aac gag							1433
Val Gly Gly Leu Met Thr Asp Gly Leu Arg Arg Leu Ser Gly Asn Glu							
393		398		403		408	
tat gtg ttt act aag aat gtg cac cag agt cac agt cac ctt gca atg							1481
Tyr Val Phe Thr Lys Asn Val His Gln Ser His Ser His Leu Ala Met							
409		414		419		424	
cca ata acc atc aat gat gtt ccc cct tgt atc tct caa tta ctt gat							1529
Pro Ile Thr Ile Asn Asp Val Pro Pro Cys Ile Ser Gln Leu Leu Asp							
425		430		435		440	
aat gag gag agt tgg gac ttc aac atc ttt gaa ttg gaa gcc att acg							1577
Asn Glu Glu Ser Trp Asp Phe Asn Ile Phe Glu Leu Glu Ala Ile Thr							
441		446		451		456	
cat aaa agg cca ttg gtt tat ctg ggc tta aag gtc ttc tct cgg ttt							1625
His Lys Arg Pro Leu Val Tyr Leu Gly Leu Lys Val Phe Ser Arg Phe							
457		462		467		472	
gga gta tgt gag ttt tta aac tgt tct gaa acc act ctt cgg gcc tgg							1673
Gly Val Cys Glu Phe Leu Asn Cys Ser Glu Thr Thr Leu Arg Ala Trp							
473		478		483		488	
ttc caa gtg atc gaa gcc aac tac cac tct tcc aat gcc tac cac aac							1721
Phe Gln Val Ile Glu Ala Asn Tyr His Ser Ser Asn Ala Tyr His Asn							
489		494		499		504	
tcc acc cat gct gcc gac gtc ctg cac gcc acc gct ttc ttt ctt gga							1769
Ser Thr His Ala Ala Asp Val Leu His Ala Thr Ala Phe Phe Leu Gly							
505		510		515		520	
aag gaa aga gta aag gga agc ctc gat cag ttg gat gag gtg gca gcc							1817
Lys Glu Arg Val Lys Gly Ser Leu Asp Gln Leu Asp Glu Val Ala Ala							
521		526		531		536	



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gac cta aag tgc aaa agt ttg agg ctt cca tct gac agc taa agccaag      2538
Asp Leu Lys Cys Lys Ser Leu Arg Leu Pro Ser Asp Ser  *
761                               766                               771

ccacagaggg ggctcttga ccgacaaagg acactgtgaa tcacagtagc gtaaacaaga      2598
ggccttcctt tctaatagaca atgacaggta ttgggtgaagg agctaattgtt taatatttga      2658
ccttgaatca ttcaagtccc caaatttcat tcttagaaag ttatgttcca tgaagaaaaa      2718
tatatgttct tttgaatact taatgacaga acaaatactt ggcaaactcc tttgctctgc      2778
tgtcatcctg tgtacccttg tcaatccatg gagctgggtc actgtaacta gcaggccaca      2838
ggaagcaaag ccttggtgcc tgtgagctca tctcccagga tgggtgactaa gtagcttagc      2898
tagtgatcag ctcatccttt accataaaag tcatcattgc tgtttagctt gactgttttc      2958
ctcaagaaca tcgatctgaa ggattcataa ggagcttatt tgaacagatt tatctaagaa      3018
aaaaaaaaaa                                                                3028

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<212> DNA
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tgtttggata ttttgaagtc acatagacac caactaatat ctgtcaccca ctgtgtcatc      180
ggatggatcg ggtgacactc caaatcagtc gtgcaggtag ttctgagtgt gcagccatta      240
gccaatgttg agtcacctca tgttgcacgt gttggctgac tggctgcctt tccccctgcc      300
agggagaagc gcattggcat tgacctggtg cacgacacag tggagcatga gctgataaag      360
gaggctgaga tcatccaggg catt      atg gct ctg ctg acc cgt acc ttg gag      411
                                Met Ala Leu Leu Thr Arg Thr Leu Glu
                                1                               5

gag gct tcc gag cag att cgg atg aac cgc tct gcc aag tac aat ctt      459

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234	239	244	249	
tcc atc cca ctt cgg gat ggg gaa gac cat ggg gtc tgg gct ggg ggc				1179
Ser Ile Pro Leu Arg Asp Gly Glu Asp His Gly Val Trp Ala Gly Gly				
250	255	260	265	
ctc cgc cct gat gct gtc tgc taa tagtagggct agttccaatt ctcattaaac				1233
Leu Arg Pro Asp Ala Val Cys *				
266	271			
cacattgtaa acagtaaaaa aaaaaa				1259

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gctgggtacg cgtaagcttg ggcccctcga gggatactct agagcggccg cccgggagtc	120
cgagcgccag ctgcgctcc gcctctgcgt cctcaacgag atcttgggca ccgagaggga	180
ctacgtgggc accttgcgt tcttgcagtc ggcattcctg catcgcatcc ggcagaacgt	240
ggccgactca gtggagaagg gcctcacgga ggagaatgtc aaggctcctgt tctcgaacat	300
cgaagacatc ctggaagttc ataaggattt cttggccgcc ttggagtatt gtttacaccc	360
ggagccgcag tctcagcatg aacttgggaa tgttttctta aaattcaagg acaagttctg	420
cgtgtacgag gagtattgca gcaaccatga gaaagccctg aggctgctgg tggagctgaa	480
caagatccct accgtgcgcg ccttcctttt gagctgc atg ctt ctg gga ggc cgg	535
Met Leu Leu Gly Gly Arg	
1	

aag acc acg gac atc cct ttg gaa ggc tac ctg ttg tct ccg atc cag	583
Lys Thr Thr Asp Ile Pro Leu Glu Gly Tyr Leu Leu Ser Pro Ile Gln	
7 12 17 22	

agg atc tgc aag tac ccg ctc ctc ctt aag gag ctg gcc aag agg act	631
Arg Ile Cys Lys Tyr Pro Leu Leu Leu Lys Glu Leu Ala Lys Arg Thr	
23 28 33 38	

ccc ggc aag cac cca gac cac ccc gcg gtc cag agt gcc ctg cag gcc	679
Pro Gly Lys His Pro Asp His Pro Ala Val Gln Ser Ala Leu Gln Ala	
39 44 49 54	











Phe	Leu	Glu	Ile	Ser	Ser	Tyr	Tyr	Asp	Pro	Gly	Arg	Leu	Ile	Cys	Asp	
656					661					666					671	
ttt	ccc	ttt	gat	ggc	ctc	tta	gaa	gaa	cga	gct	ctc	ctg	ttg	ggg	cgc	2242
Phe	Pro	Phe	Asp	Gly	Leu	Leu	Glu	Glu	Arg	Ala	Leu	Leu	Leu	Gly	Arg	
672					677					682					687	
atg	ggg	aaa	cat	gaa	caa	gct	ctt	ttc	att	tat	gtc	cac	atc	ttg	aag	2290
Met	Gly	Lys	His	Glu	Gln	Ala	Leu	Phe	Ile	Tyr	Val	His	Ile	Leu	Lys	
688					693					698					703	
gat	aca	agg	atg	gct	gag	gag	tac	tgc	cac	aaa	cac	tat	gac	cga	aac	2338
Asp	Thr	Arg	Met	Ala	Glu	Glu	Tyr	Cys	His	Lys	His	Tyr	Asp	Arg	Asn	
704					709					714					719	
aaa	gat	ggc	aac	aaa	gat	gtg	tat	ctg	tcc	ctg	ctt	cgg	atg	tac	ctg	2386
Lys	Asp	Gly	Asn	Lys	Asp	Val	Tyr	Leu	Ser	Leu	Leu	Arg	Met	Tyr	Leu	
720					725					730					735	
tcg	ccc	ccc	agc	att	cac	tgc	ctg	ggg	cca	atc	aag	ctg	gaa	cta	ctg	2434
Ser	Pro	Pro	Ser	Ile	His	Cys	Leu	Gly	Pro	Ile	Lys	Leu	Glu	Leu	Leu	
736					741					746					751	
gag	cca	aaa	gcc	aac	ctc	cag	gcc	gct	ctg	cag	gtc	ctc	gag	cta	cac	2482
Glu	Pro	Lys	Ala	Asn	Leu	Gln	Ala	Ala	Leu	Gln	Val	Leu	Glu	Leu	His	
752					757					762					767	
cac	agc	aaa	ctg	gac	acc	acc	aag	gcc	ctc	aac	ctt	ctg	cca	gca	aac	2530
His	Ser	Lys	Leu	Asp	Thr	Thr	Lys	Ala	Leu	Asn	Leu	Leu	Pro	Ala	Asn	
768					773					778					783	
act	cag	atc	aat	gac	ata	cgc	atc	ttc	ctg	gaa	aag	gtc	ttg	gaa	gaa	2578
Thr	Gln	Ile	Asn	Asp	Ile	Arg	Ile	Phe	Leu	Glu	Lys	Val	Leu	Glu	Glu	
784					789					794					799	
aat	gca	caa	aag	aaa	cgg	ttc	aat	caa	gtg	ctc	aag	aac	ctt	ctc	cat	2626
Asn	Ala	Gln	Lys	Lys	Arg	Phe	Asn	Gln	Val	Leu	Lys	Asn	Leu	Leu	His	
800					805					810					815	
gca	gaa	ttc	ctg	agg	gtc	cag	gaa	gag	cgg	att	tta	cac	cag	cag	gtg	2674
Ala	Glu	Phe	Leu	Arg	Val	Gln	Glu	Glu	Arg	Ile	Leu	His	Gln	Gln	Val	
816					821					826					831	
aag	tgc	atc	atc	aca	gag	gag	aag	gtg	tgc	atg	gtg	tgt	aag	aag	aag	2722
Lys	Cys	Ile	Ile	Thr	Glu	Glu	Lys	Val	Cys	Met	Val	Cys	Lys	Lys	Lys	
832					837					842					847	
att	ggg	aac	agt	gca	ttt	gca	aga	tac	ccc	aat	gga	gtg	gtc	gtc	cat	2770
Ile	Gly	Asn	Ser	Ala	Phe	Ala	Arg	Tyr	Pro	Asn	Gly	Val	Val	Val	His	
848					853					858					863	
tac	ttc	tgt	tcc	aaa	gag	gta	aac	cca	gct	gac	act	tga	gcccagcatc			2819
Tyr	Phe	Cys	Ser	Lys	Glu	Val	Asn	Pro	Ala	Asp	Thr	*				
864					869					874						
ctggggatcc	agcggatgga	cagcttggt	ctcccagaga	ggtgaaggag	cacctggcct											2879



ctgtgcttgt tatcttccat tctcaciaaac tgtcttttgaa gcaatagaat aaagaatgtg 4679  
 tgttttcttt cctggtatac atacatgata ccatgctccc aagctccatt cttccttccc 4739  
 tcaactctct gccctccaca gagctatgga gaaggctgga gatgaaagct ttgtagtgag 4799  
 gactgataaa gatctcatca ctgctcctta taataaacct aataaagcaa gaaaaaaaaa 4859  
 aaa 4862

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 <213> Homo sapiens

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 <222> (69)..(1064)

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 Met Ser Arg Ala Arg Gly Ala Leu Cys Arg Ala Cys Leu Ala  
 1 5 10  
 ctg gcc gcg gcc ctg gcc gcg ctg ctg tta ctg ccg ctg ccg ctg ccc 158  
 Leu Ala Ala Ala Leu Ala Ala Leu Leu Leu Leu Pro Leu Pro Leu Pro  
 15 20 25 30  
 cgc gcg ccc gcc ccg gcc cgg acc ccc gcc ccg gcc ccg cgc gcg ccc 206  
 Arg Ala Pro Ala Pro Ala Arg Thr Pro Ala Pro Ala Pro Arg Ala Pro  
 31 36 41 46  
 ccg tcc cgg ccc gct gcc ccc agc ctg cgg cct gac gac gtc ttc atc 254  
 Pro Ser Arg Pro Ala Ala Pro Ser Leu Arg Pro Asp Asp Val Phe Ile  
 47 52 57 62  
 gcc gtc aag acc acc cgg aag aac cac ggg ccg cgc ctg cgg ctg ctg 302  
 Ala Val Lys Thr Thr Arg Lys Asn His Gly Pro Arg Leu Arg Leu Leu  
 63 68 73 78  
 ctg cgc acc tgg atc tcc cgg gcc cgc cag cag acg ttt atc ttc acc 350  
 Leu Arg Thr Trp Ile Ser Arg Ala Arg Gln Gln Thr Phe Ile Phe Thr  
 79 84 89 94  
 gac ggg gac gac cct gag ctc gag ctc cag ggc ggc gac cgt gtc atc 398  
 Asp Gly Asp Asp Pro Glu Leu Glu Leu Gln Gly Gly Asp Arg Val Ile  
 95 100 105 110  
 aac acc aac tgc tcg gcg gtg cgc act cgt cag gcc ctc tgc tgc aag 446  
 Asn Thr Asn Cys Ser Ala Val Arg Thr Arg Gln Ala Leu Cys Cys Lys  
 111 116 121 126

atg tcc gtg gag tat gac aag ttc att gag tcc ggg cgc aag tgg ttt	494
Met Ser Val Glu Tyr Asp Lys Phe Ile Glu Ser Gly Arg Lys Trp Phe	
127 132 137 142	
tgc cac gtg gat gat gac aat tat gtg aac gca agg agc ctc ctg cac	542
Cys His Val Asp Asp Asp Asn Tyr Val Asn Ala Arg Ser Leu Leu His	
143 148 153 158	
ctg ctc tcc agc ttc tca ccc agc cag gac gtc tac ctg ggg cgg ccc	590
Leu Leu Ser Ser Phe Ser Pro Ser Gln Asp Val Tyr Leu Gly Arg Pro	
159 164 169 174	
agc ctg gac cac ccc att gag gcc acc gag agg gtc cag ggt ggc aga	638
Ser Leu Asp His Pro Ile Glu Ala Thr Glu Arg Val Gln Gly Gly Arg	
175 180 185 190	
act gtg acc acg gtc aag ttc tgg ttt gct act ggt ggg gcc ggg ttc	686
Thr Val Thr Thr Val Lys Phe Trp Phe Ala Thr Gly Gly Ala Gly Phe	
191 196 201 206	
tgc ctc agc aga ggc ctt gcc ctc aag atg agc cca tgg gcc agc ctg	734
Cys Leu Ser Arg Gly Leu Ala Leu Lys Met Ser Pro Trp Ala Ser Leu	
207 212 217 222	
ggc agc ttc atg agc aca gct gag cag gtg cgg ctg ccg gat gac tgc	782
Gly Ser Phe Met Ser Thr Ala Glu Gln Val Arg Leu Pro Asp Asp Cys	
223 228 233 238	
aca gtt ggc tac atc gtg gag ggg ctc ctg ggc gcc cgc ctg ctg cac	830
Thr Val Gly Tyr Ile Val Glu Gly Leu Leu Gly Ala Arg Leu Leu His	
239 244 249 254	
agc ccc ctc ttc cac tct cac ctg gag aac ctg cag agg ctg ccg ccc	878
Ser Pro Leu Phe His Ser His Leu Glu Asn Leu Gln Arg Leu Pro Pro	
255 260 265 270	
gac acc ctg ctc cag cag gtt acc ttg agc cat ggg ggt cct gag aac	926
Asp Thr Leu Leu Gln Gln Val Thr Leu Ser His Gly Gly Pro Glu Asn	
271 276 281 286	
cca cag aac gtg gtg aac gtg gct gga ggc ttc agc ctg cat caa gac	974
Pro Gln Asn Val Val Asn Val Ala Gly Gly Phe Ser Leu His Gln Asp	
287 292 297 302	
ccc aca cgg ttt aag tct atc cat tgt ctt ctg tac cca gac acg gac	1022
Pro Thr Arg Phe Lys Ser Ile His Cys Leu Leu Tyr Pro Asp Thr Asp	
303 308 313 318	
tgg tgt ccc agg cag aaa cag ggc gcc ccg acc tct cgg tga caccaac	1071
Trp Cys Pro Arg Gln Lys Gln Gly Ala Pro Thr Ser Arg *	
319 324 329	
caccccgacc cagggctgcc tggctctgtc ccaggcgagg ggaaccagag cccctatgg	1131
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<213> Homo sapiens

<220>

<221> CDS

<222> (158)..(907)

<400> 59

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actgaagata agaaagatct gagtggatca gaggaag atg tta ttg aag gtg cag	175
Met Leu Leu Lys Val Gln	
1	
tac atc tca tgt tgg gca gtg atg tcc ttc agt tca ttt gtt ttg aac	223
Tyr Ile Ser Cys Trp Ala Val Met Ser Phe Ser Ser Phe Val Leu Asn	
7 12 17 22	
cca ttg aga cta tcg tac aac tta gtt tgt aaa gca ttt tca ggt atg	271
Pro Leu Arg Leu Ser Tyr Asn Leu Val Cys Lys Ala Phe Ser Gly Met	
23 28 33 38	
gtc ttc cct ccc ccg gta ttt gtg gtt aca gaa cct gct gac acg gat	319
Val Phe Pro Pro Pro Val Phe Val Val Thr Glu Pro Ala Asp Thr Asp	
39 44 49 54	
ggc cag ctg tac ttg tgt ttc tca ttt gat cct tat att gca gta tcg	367
Gly Gln Leu Tyr Leu Cys Phe Ser Phe Asp Pro Tyr Ile Ala Val Ser	
55 60 65 70	
gag tta cag aag ctt att cgg caa ctc ttg ctt ttg cag tta ttt cca	415
Glu Leu Gln Lys Leu Ile Arg Gln Leu Leu Leu Leu Gln Leu Phe Pro	
71 76 81 86	
aaa tat ctg ata tat att gac att aac aag gct ctt ctt gcc aag aga	463
Lys Tyr Leu Ile Tyr Ile Asp Ile Asn Lys Ala Leu Leu Ala Lys Arg	
87 92 97 102	
aag aga cta gaa atg tat acc aag gct tct ctc aaa act agt aac cag	511
Lys Arg Leu Glu Met Tyr Thr Lys Ala Ser Leu Lys Thr Ser Asn Gln	
103 108 113 118	
aaa att gaa cat gtt tgg aaa aca caa caa gat caa agg cag aag ctt	559
Lys Ile Glu His Val Trp Lys Thr Gln Gln Asp Gln Arg Gln Lys Leu	
119 124 129 134	
aac caa gaa tat tct cag cag ttt ctg act ttg ttt cag cag tgg gat	607
Asn Gln Glu Tyr Ser Gln Gln Phe Leu Thr Leu Phe Gln Gln Trp Asp	
135 140 145 150	
tta gat atg cag aaa gct gag gaa caa gaa gaa aaa ata ctt aat atg	655
Leu Asp Met Gln Lys Ala Glu Glu Gln Glu Glu Lys Ile Leu Asn Met	
151 156 161 166	
ttt cga cag caa caa aag att ctt caa caa tct aga att gtt cag agc	703
Phe Arg Gln Gln Gln Lys Ile Leu Gln Gln Ser Arg Ile Val Gln Ser	













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2624

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<212> DNA  
<213> Homo sapiens

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<222> (1)..(2565)

<400> 62

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1 5 10	
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Gly Val Ser His Arg Ala Gly Ser Arg Asp Cys Leu Pro Pro Ala Ala	
17 22 27 32	
tgc ttt cgg agg cgg cgg ctg gca cgg agg ccg ggc tac atg aga agc	144
Cys Phe Arg Arg Arg Arg Leu Ala Arg Arg Pro Gly Tyr Met Arg Ser	
33 38 43 48	
tcg aca ggg cct ggg atc ggg ttc ctt tcc cca gca gtg ggc aca ctg	192
Ser Thr Gly Pro Gly Ile Gly Phe Leu Ser Pro Ala Val Gly Thr Leu	
49 54 59 64	
ttc cgg ttc cca gga ggg gtg tct ggc gag gag tcc cac cac tcg gag	240
Phe Arg Phe Pro Gly Gly Val Ser Gly Glu Glu Ser His His Ser Glu	
65 70 75 80	
tcc agg gcc aga cag tgt ggc ctt gac tcg aga ggc ctc ttg gtc cgg	288
Ser Arg Ala Arg Gln Cys Gly Leu Asp Ser Arg Gly Leu Leu Val Arg	
81 86 91 96	
agc cct gtt tcc aag agt gca gca gcc cct act gtg acc tct gtg aga	336
Ser Pro Val Ser Lys Ser Ala Ala Ala Pro Thr Val Thr Ser Val Arg	
97 102 107 112	
gga acc tcg gcg cac ttt ggg att cag ctc aga ggt ggc acc aga ttg	384
Gly Thr Ser Ala His Phe Gly Ile Gln Leu Arg Gly Gly Thr Arg Leu	
113 118 123 128	
cct gac agg ctt agc tgg ccg tgt ggc cct ggg agt gct ggg tgg cag	432
Pro Asp Arg Leu Ser Trp Pro Cys Gly Pro Gly Ser Ala Gly Trp Gln	
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Gln Glu Phe Ala Ala Met Asp Ser Ser Glu Thr Leu Asp Ala Ser Trp	
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gag gca gcc tgc agc gat gga gca agg cgt gtc cgg gca gca ggc tct	528

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Leu	Pro	Ser	Ala	Glu	Leu	Ser	Ser	Asn	Ser	Cys	Ser	Pro	Gly	Cys	Gly		
177					182					187					192		
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Pro	Glu	Val	Pro	Pro	Thr	Pro	Pro	Gly	Ser	His	Ser	Ala	Phe	Thr	Ser		
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Ser	Phe	Ser	Phe	Ile	Arg	Leu	Ser	Leu	Gly	Ser	Ala	Gly	Glu	Arg	Gly		
209					214					219					224		
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Glu	Ala	Glu	Gly	Cys	Pro	Pro	Ser	Arg	Glu	Ala	Glu	Ser	His	Cys	Gln		
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Ser	Pro	Gln	Glu	Met	Gly	Ala	Lys	Ala	Ala	Ser	Leu	Asp	Gly	Pro	His		
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Glu	Asp	Pro	Arg	Cys	Leu	Ser	Gln	Pro	Phe	Ser	Leu	Leu	Ala	Thr	Arg		
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Val	Ser	Ala	Asp	Leu	Ala	Gln	Ala	Ala	Arg	Asn	Ser	Ser	Arg	Pro	Glu		
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Arg	Asp	Met	His	Ser	Leu	Pro	Asp	Met	Asp	Pro	Gly	Ser	Ser	Ser	Ser		
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Gly	Asp	Ala	His	Ser	Trp	Asp	Thr	Leu	Leu	Arg	Lys	Trp	Glu	Pro	Val		
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Asp	Tyr	Asp	Lys	Ala	Glu	Thr	Leu	Gln	Gln	Arg	Leu	Glu	Asp	Leu	Glu		
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caa	gag	aaa	atc	agc	ctg	cac	ttt	caa	ctt	cct	tca	agg	cag	cca	gct		1200
Gln	Glu	Lys	Ile	Ser	Leu	His	Phe	Gln	Leu	Pro	Ser	Arg	Gln	Pro	Ala		





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 Gly Gly Gly Gly Asn Ser Thr Ala Ala Ala Ala Gly Gly Asn Gln Lys  
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 Asn Ser Pro Asp Arg Val Lys Arg Pro Met Asn Ala Phe Met Val Trp  
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 Ser Arg Gly Gln Arg Arg Lys Met Ala Gln Glu Asn Pro Lys Met His  
 52 57 62 67

aac tcg gag atc agc aag cgc ctg ggc gcc gag tgg aaa ctt ttg tcg 294  
 Asn Ser Glu Ile Ser Lys Arg Leu Gly Ala Glu Trp Lys Leu Leu Ser  
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gag acg gag aag cgg ccg ttc atc gac gag gct aag cgg ctg cga gcg 342  
 Glu Thr Glu Lys Arg Pro Phe Ile Asp Glu Ala Lys Arg Leu Arg Ala  
 84 89 94 99

ctg cac atg aag gag cac ccg gat tat aaa tac cgg ccc cgg cgg aaa 390  
 Leu His Met Lys Glu His Pro Asp Tyr Lys Tyr Arg Pro Arg Arg Lys  
 100 105 110 115

acc aag acg ctc atg aag aag gat aag tac acg ctg ccc ggc ggg ctg 438  
 Thr Lys Thr Leu Met Lys Lys Asp Lys Tyr Thr Leu Pro Gly Gly Leu  
 116 121 126 131

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Glu	Pro	Leu	Phe	Pro	Gly	Ser	Arg	Arg	Ser	Arg	Ser	Val	Trp	Asp	Ala	
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Val	Arg	Leu	Glu	Val	Gly	Val	Pro	Asp	Ser	Cys	Pro	Val	Val	Leu	His	
33					38					43					48	
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Ser	Phe	Thr	Gln	Leu	Asp	Pro	Asp	Leu	Pro	Arg	Pro	Glu	Ser	Ser	Thr	
49					54					59					64	
cag	gag	atc	ggc	gag	gag	ctg	atc	aac	gga	gtc	atc	tac	tcc	atc	tcc	240
Gln	Glu	Ile	Gly	Glu	Glu	Leu	Ile	Asn	Gly	Val	Ile	Tyr	Ser	Ile	Ser	
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97					102					107					112	
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Val	Pro	Ala	Phe	Gln	Gly	Ser	Asp	Leu	Ser	Tyr	Val	Thr	Ile	Phe	Leu	
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Trp Ser Asp Arg Gln Ala Pro Ser Thr Glu Leu Ser Thr Ser Gly Ser							
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Ser His Ser Lys Ser Cys Asp Gln Leu Arg Cys Gly Pro Tyr Leu Ser							
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Ser Gly Asp Ile Ala Asp Ala Leu Ser Val His Ser Ala Gly Ser Ser							
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Ser Ser Asp Val Glu Glu Ile Asn Ile Ser Phe Val Pro Glu Ser Pro							
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gat ggc cag gaa aag aag ttc tgg gaa tca gcc tca cag tca tcc ccg	2256						
Asp Gly Gln Glu Lys Lys Phe Trp Glu Ser Ala Ser Gln Ser Ser Pro							
737		742		747		752	
gag acc tcc ggc atc agc tca gcc tcc agc agc acc tcg tcc tcc tca	2304						
Glu Thr Ser Gly Ile Ser Ser Ala Ser Ser Ser Thr Ser Ser Ser Ser							
753		758		763		768	
gcc tcc acc acg ccc gtg gct gcc aca cgc acc cac aag cgc tct gtc	2352						
Ala Ser Thr Thr Pro Val Ala Ala Thr Arg Thr His Lys Arg Ser Val							
769		774		779		784	
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Ser Gly Leu Cys Asn Ser Ser Ser Ala Leu Pro Leu Tyr Asn Gln Gln							
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Val Gly Asp Cys Cys Ile Ile Arg Val Ser Leu Asp Val Asp Asn Gly							
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817		822		827		832	
gta atc cgc aag gcc atg gac aaa cac aac ctg gag gag gag gag ccg	2544						
Val Ile Arg Lys Ala Met Asp Lys His Asn Leu Glu Glu Glu Glu Pro							
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Glu Asp Tyr Glu Leu Leu Gln Ile Leu Ser Asp Asp Arg Lys Leu Lys							
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Ile Pro Glu Asn Ala Asn Val Phe Tyr Ala Met Asn Ser Thr Ala Asn							
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Tyr Asp Phe Val Leu Lys Lys Arg Thr Phe Thr Lys Gly Val Lys Val							
881		886		891		896	

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 913 918

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Lys Thr Tyr Leu Ser Arg Pro Pro Thr Glu Gln Leu Leu Lys Phe Pro	
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Phe Ile Arg Asp Gln Pro Thr Glu Arg Gln Val Arg Ile Gln Leu Lys	
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Cys Tyr Glu Asp Glu Gly Val Tyr Val Asn Thr Tyr Gly Arg Ile Ile	
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Ile Cys Ser Asn Gln Ile Met Gly Trp Gly Glu Lys Ala Ile Glu Ile	
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                                   Met Asn Gly Ile Arg Leu Gly
                                   1                               5

acc tat ggg ctg gct gag gct ggg ggc tac ctg cac aca gcc gaa ggc      161
Thr Tyr Gly Leu Ala Glu Ala Gly Gly Tyr Leu His Thr Ala Glu Gly
      8                               13                               18                               23

acc cac agt cct gcc cgc agc gca gca gct ggg gcc atg gct ggg gtc      209
Thr His Ser Pro Ala Arg Ser Ala Ala Ala Gly Ala Met Ala Gly Val
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atg gga gcc tac ttg ggg agc ccc atc tac atg gtg aag aca cac ctg      257
Met Gly Ala Tyr Leu Gly Ser Pro Ile Tyr Met Val Lys Thr His Leu
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cag gca cag gca gcc tca gaa att gct gta ggg cac cag tat aag cat      305
Gln Ala Gln Ala Ala Ser Glu Ile Ala Val Gly His Gln Tyr Lys His
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cag ggc atg ttt cag gcg cta acc gag att ggc cag aaa cat ggt ctg      353
Gln Gly Met Phe Gln Ala Leu Thr Glu Ile Gly Gln Lys His Gly Leu
      72                               77                               82                               87

gtg ggg tta tgg cgt ggg gct ctg ggc ggc ctg ccc cga gtt atc gtc      401
Val Gly Leu Trp Arg Gly Ala Leu Gly Gly Leu Pro Arg Val Ile Val
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ggt tcc tcc acc cag ctg tgc acc ttc tca tcc acc aag gac ctc ctg      449
Gly Ser Ser Thr Gln Leu Cys Thr Phe Ser Ser Thr Lys Asp Leu Leu
      104                               109                               114                               119

agc cag tgg gag atc ttt cct ccc cag agc tgg aag ttg gcg ctg gtg      497
Ser Gln Trp Glu Ile Phe Pro Pro Gln Ser Trp Lys Leu Ala Leu Val
      120                               125                               130                               135

gct gcc atg atg agt ggc att gca gtt gtc ttg gcc atg gca ccc ttt      545
Ala Ala Met Met Ser Gly Ile Ala Val Val Leu Ala Met Ala Pro Phe
      136                               141                               146                               151

gat gtg gcc tgc aca agg ctc tac aac cag ccc aca gat gca cag ggc      593

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Lys	Gly	Leu	Met	Tyr	Arg	Gly	Ile	Leu	Asp	Ala	Leu	Leu	Gln	Thr	Ala	
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Arg	Thr	Glu	Gly	Ile	Phe	Gly	Met	Tyr	Lys	Gly	Ile	Gly	Ala	Ser	Tyr	
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Phe	Arg	Leu	Gly	Pro	His	Thr	Ile	Leu	Ser	Leu	Phe	Phe	Trp	Asp	Gln	
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Leu	Arg	Ser	Leu	Tyr	Tyr	Thr	Asp	Thr	Lys	*						
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cagcgttcgc cgcgccgggc cggggtggcg ggccggcccc ggaccggggc agctggagaa	240
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Glu Lys Arg Arg Asn Pro Ser Lys His Tyr Val Tyr Ile Ile Asn Val	
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Thr Trp Ser Asp Ser Thr Ser Gln Thr Ile Tyr Arg Arg Tyr Ser Lys	
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Phe Phe Asp Leu Gln Met Gln Leu Leu Asp Lys Phe Pro Ile Glu Gly	
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Gly Gln Lys Asp Pro Lys Gln Arg Ile Ile Pro Phe Leu Pro Gly Lys	
63 68 73 78	
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Ile Leu Phe Arg Arg Ser His Ile Arg Asp Val Ala Val Lys Arg Leu	
79 84 89 94	
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Lys Pro Ile Asp Glu Tyr Cys Arg Ala Leu Val Arg Leu Pro Pro His	
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Ile Ser Gln Cys Asp Glu Val Phe Arg Phe Phe Glu Ala Arg Pro Glu	
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Asp Val Asn Pro Pro Lys Glu Gln Gly Pro Ser Pro Pro Asp Ala Val	
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Leu Pro Tyr Gly Val Asn Lys Gly Lys Gln Glu Leu Lys Ala Gly Pro	
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Asn Trp Pro Gly Arg Thr His His Val Val Asn Cys Val Thr Gln Lys	
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 Ala Thr Gln Gln Asp Ala Asn Ala Ser Ser Leu Leu Asp Ile Tyr Ser  
 40 45 50 55  
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 Phe Trp Leu Lys Ser Ala Lys Val Pro Glu Arg Lys Leu Gln Ala Asn  
 56 61 66 71  
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 Gly Pro Val Ala Lys Lys Ala Lys Lys Lys Ala Ser Ser Ser Asp Ser  
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 Lys Ala Ala Val Pro Ala Lys Arg Val Gly Leu Pro Pro Gly Lys Ala  
 104 109 114 119  
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Pro	Arg	Trp	Lys	Lys	Asp	Ser	Val	Thr	Ala	Ile	Leu	Gly	Lys	Asn	Glu	
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Ser	Trp	Glu	Thr	His	Leu	Ala	Pro	Thr	Ala	Pro	Pro	Asn	Gly	Leu	Thr	
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Ser	Ala	Ala	Asp	Ala	Ile	Lys	Ser	Gln	Asp	Phe	Lys	Asp	Thr	Ala	Gly	
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Gln	Arg	Val	Pro	Gly	Pro	Lys	Asp	Pro	Ala	Glu	Leu	Thr	Tyr	Tyr	Thr	
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Arg Lys Arg Asn Val Pro Ala Ser Asp Glu Glu Glu Gly Ala Val Leu				
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Phe Asp Asn Ser Ser Lys Val Ala Ala Glu Pro Phe Asp Thr Ser Ser				
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Phe Val Ile Ile Phe Leu Gly Val Val Leu Val Met Lys Lys Arg Lys	
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Leu Ala Lys Lys Arg Lys Glu Thr Met Ser Ser Thr Arg Gln Glu Met	
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Ala	Ser	Asp	Thr	Ser	Ser	Leu	Val	Gln	Ser	His	Thr	Tyr	Lys	Lys	Arg	
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Cys	Lys	Tyr	Trp	Pro	Asp	Asp	Thr	Glu	Ile	Tyr	Lys	Asp	Ile	Lys	Val	
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Cys Tyr Glu Val Ala Leu Glu Tyr Leu Asn Ser Gly *	
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Ser Asp Ser Asn Ala Ser Phe Leu Arg Ala Ala Arg Ala Gly Asn Leu
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Asp Lys Val Val Glu Tyr Leu Lys Gly Gly Ile Asp Ile Asn Thr Cys
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Asn Gln Asn Gly Leu Asn Ala Leu His Leu Ala Ala Lys Glu Gly His
 61              66              71              76

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Val Gly Leu Val Gln Glu Leu Leu Gly Arg Gly Ser Ser Val Asp Ser
 77              82              87              92

gcc act aag aag gga aat acc gct ctt cac att gca tct ttg gct gga 339
Ala Thr Lys Lys Gly Asn Thr Ala Leu His Ile Ala Ser Leu Ala Gly
 93              98              103              108

caa gca gaa gtt gtc aaa gtt ctt gtt aag gaa gga gcc aat att aat 387
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Tyr	Leu	Thr	Ala	Leu	His	Val	Ala	Ala	His	Cys	Gly	His	Tyr	Arg	Val	
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Thr	Lys	Leu	Leu	Leu	Asp	Lys	Arg	Ala	Asn	Pro	Asn	Ala	Arg	Ala	Leu	
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Val	Met	Glu	Leu	Leu	Val	Lys	Tyr	Gly	Ala	Ser	Ile	Gln	Ala	Ile	Thr	
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Asn	Ile	Val	Leu	Leu	Leu	Leu	Gln	Asn	Gly	Ala	Ser	Pro	Asp	Val	Thr	
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Asn	Ile	Arg	Gly	Glu	Thr	Ala	Leu	His	Met	Ala	Ala	Arg	Ala	Gly	Gln	
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Val	Glu	Val	Val	Arg	Cys	Leu	Leu	Arg	Asn	Gly	Ala	Leu	Val	Asp	Ala	
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Gly	Gln	Val	Asp	Val	Ala	Ser	Val	Leu	Leu	Glu	Ala	Gly	Ala	Ala	His	
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tcc	tta	gct	acc	aag	aag	ggc	ttt	act	ccc	ctg	cat	gta	gca	gcc	aag	1731
Ser	Leu	Ala	Thr	Lys	Lys	Gly	Phe	Thr	Pro	Leu	His	Val	Ala	Ala	Lys	
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Tyr	Gly	Ser	Leu	Asp	Val	Ala	Lys	Leu	Leu	Leu	Gln	Arg	Arg	Ala	Ala	

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His Tyr Asp Asn Gln Lys Val Ala Leu Leu Leu Leu Glu Lys Gly Ala				
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His Gly Ala Asp Gln Asp Ala His Thr Lys Leu Gly Tyr Thr Pro Leu				
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Leu His Gln Ala Ala Gln Gln Gly His Thr His Ile Ile Asn Val Leu				
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acg aga ggc ctg gtg cat caa gct att tgc aac tta aac atc act ttg	4371
Thr Arg Gly Leu Val His Gln Ala Ile Cys Asn Leu Asn Ile Thr Leu	
1437 1442 1447 1452	
ccg att tat aca aag gaa tca gag tca gat caa gaa cag gag gaa gag	4419
Pro Ile Tyr Thr Lys Glu Ser Glu Ser Asp Gln Glu Gln Glu Glu Glu	
1453 1458 1463 1468	
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Ile Asp Met Thr Ser Glu Lys Asn Pro Gln Asp Glu Gln Glu Arg Ile	
1469 1474 1479 1484	
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Glu Glu Arg Leu Ala Tyr Ile Ala Asp His Leu Gly Phe Ser Trp Thr	

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Glu Leu Ala Arg Glu Leu Asp Phe Thr Glu Glu Gln Ile His Gln Ile							
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Arg Ile Glu Asn Pro Asn Ser Leu Gln Asp Gln Ser His Ala Leu Leu							
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Lys Tyr Trp Leu Glu Arg Asp Gly Lys His Ala Thr Asp Thr Asn Leu							
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Val Glu Cys Leu Thr Lys Ile Asn Arg Met Asp Ile Val His Leu Met							
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Glu Thr Asn Thr Glu Pro Leu Gln Glu Arg Ile Ser His Ser Tyr Ala							
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Glu Ile Glu Gln Thr Ile Thr Leu Asp His Ser Glu Gly Phe Ser Val							
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Leu Gln Glu Glu Leu Cys Thr Ala Gln His Lys Gln Lys Glu Glu Gln							
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Ala Val Ser Lys Glu Ser Glu Thr Cys Asp His Pro Pro Ile Val Ser							
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Glu Glu Asp Ile Ser Val Gly Tyr Ser Thr Phe Gln Asp Gly Val Pro							
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Lys Thr Glu Gly Asp Ser Ser Ser Thr Ala Leu Phe Pro Gln Thr His							
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Lys Glu Gln Val Gln Gln Asp Phe Ser Gly Lys Met Gln Asp Leu Pro							
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Glu Glu Ser Ser Leu Glu Tyr Gln Gln Glu Tyr Phe Val Thr Thr Pro							
1677		1682		1687		1692	
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Gly Thr Glu Thr Ser Glu Thr Gln Lys Ala Met Ile Val Pro Ser Ser							
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ccc agc aag aca cct gag gaa gtt agc acc cct gca gag gag gag aag							5187
Pro Ser Lys Thr Pro Glu Glu Val Ser Thr Pro Ala Glu Glu Glu Lys							
1709		1714		1719		1724	



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aatccttcca aggaatatct atgtacaatg tatatagctg aaatgctcag atgaacaaca 6214
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      Met Gly Cys Ile Met Thr Glu Ala Leu Glu Asn Lys Ser Val
          1             5             10

cat ttt ccc cta aga agt aaa tac aac agg ctt aca aaa gtt gct cgc 157
His Phe Pro Leu Arg Ser Lys Tyr Asn Arg Leu Thr Lys Val Ala Arg
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Phe Leu Gln Glu Asn Pro Ser Cys Leu Leu Cys Asn Ile Leu His His
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tat ctg cac cag gca aat tac tcc atc att gat gat gct aca atg agc 253
Tyr Leu His Gln Ala Asn Tyr Ser Ile Ile Asp Asp Ala Thr Met Ser
  47             52             57             62

gat gga ctt cct gct ttg gta act ttg aag aaa ggt tta gtt gca ctg 301
Asp Gly Leu Pro Ala Leu Val Thr Leu Lys Lys Gly Leu Val Ala Leu
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gca agg cag tgg atg aag ttt att gtg gtg aca cca gcc ttt aaa gga 349
Ala Arg Gln Trp Met Lys Phe Ile Val Val Thr Pro Ala Phe Lys Gly
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gtt agc tta cat aga cca gct cag cct ctg aaa cct caa ata gct atg 397
Val Ser Leu His Arg Pro Ala Gln Pro Leu Lys Pro Gln Ile Ala Met
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gac cat gaa cat gaa gat gga ctt gga ttg gac aat ggg ggt ggt ctt 445
Asp His Glu His Glu Asp Gly Leu Gly Leu Asp Asn Gly Gly Gly Leu
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caa agt gat acc agt gct gat gga gca gaa ttt gag ttc gat gca gcc 493
Gln Ser Asp Thr Ser Ala Asp Gly Ala Glu Phe Glu Phe Asp Ala Ala
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His	Thr	Gly	Ile	Gln	Ser	Gln	Asp	Thr	Met	Pro	Phe	Cys	Tyr	Arg	Met	
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Tyr	Phe	Gly	Glu	His	Leu	Ser	Phe	Ser	Gly	Thr	Leu	Asp	Cys	Leu	Arg	
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Ser	Val	Cys	Thr	Pro	Gln	Asn	Ser	Thr	Ser	Ala	Leu	Ser	Phe	His	Asp	
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Cys	Gln	Ser	Ile	Ser	Gln	His	Val	Asp	Met	Ala	Leu	Val	Arg	Leu	Ile	
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His	Gln	Phe	Ser	Thr	Met	Ile	Asp	Asp	Ile	Lys	Ala	Thr	Gln	Thr	Asp	
511					516					521					526	
att	aaa	ctt	agc	aga	tat	aca	gcc	gga	tct	gct	tcc	cca	aca	cct	acc	1693
Ile	Lys	Leu	Ser	Arg	Tyr	Thr	Ala	Gly	Ser	Ala	Ser	Pro	Thr	Pro	Thr	
527					532					537					542	
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Phe	Lys	Thr	Arg	Lys	His	Arg	Asp	Phe	Arg	Ser	Ser	Asp	Phe	Ser	Arg	
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agt	tct	aga	gga	agt	ctt	aat	ggt	ggc	aat	aga	gta	aat	aat	gca	aag	1789
Ser	Ser	Arg	Gly	Ser	Leu	Asn	Gly	Gly	Asn	Arg	Val	Asn	Asn	Ala	Lys	
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Asn	Lys	Arg	Thr	Asn	Asn	Glu	Asn	Asn	Lys	Lys	Glu	Ser	Arg	Asn	Lys	
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Asn	Ser	Leu	Gly	Arg	Ser	Glu	Arg	Arg	Thr	Ser	Lys	Val	Ser	Arg	Lys	



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Gly Ser Lys Asp Val	Val Asp His Met Thr	Ile His Met Asp Asp Ser																			
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Asp Ser Ile Thr Val	Ser Glu Gln Ser Glu	Pro Ser Ala Glu Cys Trp																			
623	628	633	638																		
cag aat atg tat aaa	ttg ctt aac ttc tat	tca ctt atc tcc gat cca	2029																		
Gln Asn Met Tyr Lys	Leu Leu Asn Phe Tyr	Ser Leu Ile Ser Asp Pro																			
639	644	649	654																		
aca gga ata ttg gaa	aag tct tca gaa aca	ttt gga cca gca gga gtt	2077																		
Thr Gly Ile Leu Glu	Lys Ser Ser Glu Thr	Phe Gly Pro Ala Gly Val																			
655	660	665	670																		
cgg agc cct aca gag	cca aca tgt aaa gtt	gtg ttt gag aat gaa caa	2125																		
Arg Ser Pro Thr Glu	Pro Thr Cys Lys Val	Val Phe Glu Asn Glu Gln																			
671	676	681	686																		
gac aac agc agt ttg	act aag act cag agg	aaa cgt agc ttg gta act	2173																		
Asp Asn Ser Ser Leu	Thr Lys Thr Gln Arg	Lys Arg Ser Leu Val Thr																			
687	692	697	702																		
tct gaa cct cag cat	gtt act cta ata gtg	ttt ggg att ggc atg gtg	2221																		
Ser Glu Pro Gln His	Val Thr Leu Ile Val	Phe Gly Ile Gly Met Val																			
703	708	713	718																		
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Asn Arg Thr His Leu	Glu Ala Asp Ile Gly	Gly Leu Thr Met Glu Ser																			
719	724	729	734																		
gaa ctg aag agg atc	cat ggc agt ttt act	ctt aag gaa aaa atg aaa	2317																		
Glu Leu Lys Arg Ile	His Gly Ser Phe Thr	Leu Lys Glu Lys Met Lys																			
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gat gtt tta cat caa	aag atg act gag act	tgt gct act gct cat att	2365																		
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Leu Glu Asp Phe Pro	Thr Ser Pro Thr Ser	Thr Ala Lys Gln Glu Phe																			
783	788	793	798																		
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Ala Gln Arg Gly Leu	Lys Thr Asn Asn Ala	Ala Val Phe Lys Val Gly																			
815	820	825	830																		



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cct ctc tgg aac gaa cat gat gga aca gca gat gga gat aaa cct aaa	3325
Pro Leu Trp Asn Glu His Asp Gly Thr Ala Asp Gly Asp Lys Pro Lys	
1071 1076 1081 1086	
att ctc ctc tat tcc cta aac ttg cag ttc aag ggt att caa gta acg	3373
Ile Leu Leu Tyr Ser Leu Asn Leu Gln Phe Lys Gly Ile Gln Val Thr	
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gcc act act cca tca atg aga gct gta aga ttt gaa act gga ttg att	3421
Ala Thr Thr Pro Ser Met Arg Ala Val Arg Phe Glu Thr Gly Leu Ile	
1103 1108 1113 1118	
gaa ctg gaa ctt tct aac cga ctt caa acc aaa gct tca cca gga agt	3469
Glu Leu Glu Leu Ser Asn Arg Leu Gln Thr Lys Ala Ser Pro Gly Ser	
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Ser Ser Tyr Leu Lys Leu Phe Gly Lys Cys Gln Val Asp Leu Asn Leu	
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Asp Phe His Gln Val Ala Tyr Phe Lys Thr Arg Ile Gly Leu Arg Asn	
1167 1172 1177 1182	
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Ala Leu Arg Glu Glu Ile Ser Gly Ser Ser Asp Arg Glu Ala Val Leu	
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1247 1252 1257 1262	
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Phe Gly Thr Leu Phe Leu Gln Leu Thr Val Asn Asp Leu Gly Ile Cys	
1263 1268 1273 1278	
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Glu Ile Val Lys Ala Leu Leu Gly Lys Gly Ala Gln Val Asn Ala Val				
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aat caa aat ggc tgt act ccc tta cat tat gca gct tcg aaa aac agg				294
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Lys Asp His Tyr Glu Ala Thr Ala Met His Arg Ala Ala Ala Lys Gly				
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Asn Leu Lys Met Ile His Ile Leu Leu Tyr Tyr Lys Ala Ser Thr Asn				
118	123	128	133	
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Ile Gln Asp Thr Glu Gly Asn Thr Pro Leu His Leu Ala Cys Asp Glu				
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Gln Ala Thr Asn Ser Asn Asn Arg Glu Ala Gly Ala Leu Pro Ala Cys				
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Gly Pro Arg Ala Lys Pro Trp Thr Gly Ser Phe Thr Tyr Ser Ala *				
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73 78 83 88	

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89 94 99 104	
cga gct gga cgc cac tgt ggg gct ctg aga gtc ctg aat tct tac tgg	449
Arg Ala Gly Arg His Cys Gly Ala Leu Arg Val Leu Asn Ser Tyr Trp	
105 110 115 120	
gtt ggt gaa gat tcc aca tac aaa ttt ttt gag gtt atc ctc att gat	497
Val Gly Glu Asp Ser Thr Tyr Lys Phe Phe Glu Val Ile Leu Ile Asp	
121 126 131 136	
cca ttc cat aaa gct atc aga aga aat cct gac acc cag tgg atc acc	545
Pro Phe His Lys Ala Ile Arg Arg Asn Pro Asp Thr Gln Trp Ile Thr	
137 142 147 152	
aaa cca gtc cac aag cac agg gag atg cgt ggg ctg aca tct gca ggc	593
Lys Pro Val His Lys His Arg Glu Met Arg Gly Leu Thr Ser Ala Gly	
153 158 163 168	
cga aag agc cat ggg ctt gga aag gac cgt atg ttc cac cat gct att	641
Arg Lys Ser His Gly Leu Gly Lys Asp Arg Met Phe His His Ala Ile	
169 174 179 184	
ggt ggt tct tgc cgg gca gct tag agaaggcgca aaactctcca gttccctgt	695
Gly Gly Ser Cys Arg Ala Ala *	
185 190	
taccactaat ataagtaaag tttgtaaaat tcatgcctca taatttaggg cagtcaaaaa	755
aataaataaaa taagctatatt taatattttt attctccttc aagggaccag aggccacaaa	815
agtcttgtac actatgtgtc cccagtaaata gacacataga atgnccggac gcgggggtcgc	875
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 <212> DNA  
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<220>  
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 <222> (131)..(1894)

<400> 77

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ctaaggtggg atg gat agc agg gtc tca ggc aca acc agt aat gga gag	169
Met Asp Ser Arg Val Ser Gly Thr Thr Ser Asn Gly Glu	
1 5 10	

aca	aaa	cca	gtg	tat	cca	gtc	atg	gaa	aag	aag	gag	gaa	gat	ggc	acc	217
Thr	Lys	Pro	Val	Tyr	Pro	Val	Met	Glu	Lys	Lys	Glu	Glu	Asp	Gly	Thr	
14					19					24					29	
ctg	gag	cgg	ggg	cac	tgg	aac	aac	aag	atg	gag	ttt	gtg	ctg	tca	gtg	265
Leu	Glu	Arg	Gly	His	Trp	Asn	Asn	Lys	Met	Glu	Phe	Val	Leu	Ser	Val	
30					35					40					45	
gct	ggg	gag	atc	att	ggc	tta	ggc	aac	gtc	tgg	agg	ttt	ccc	tat	ctc	313
Ala	Gly	Glu	Ile	Ile	Gly	Leu	Gly	Asn	Val	Trp	Arg	Phe	Pro	Tyr	Leu	
46					51					56					61	
tgc	tac	aaa	aat	ggg	gga	ggg	gcc	ttc	ttc	atc	ccc	tac	ctc	gtc	ttc	361
Cys	Tyr	Lys	Asn	Gly	Gly	Gly	Ala	Phe	Phe	Ile	Pro	Tyr	Leu	Val	Phe	
62					67					72					77	
ctc	ttt	acc	tgt	ggc	att	cct	gtc	ttc	ctt	ctg	gag	aca	gca	cta	ggc	409
Leu	Phe	Thr	Cys	Gly	Ile	Pro	Val	Phe	Leu	Leu	Glu	Thr	Ala	Leu	Gly	
78					83					88					93	
cag	tac	act	agc	cag	gga	ggc	gtc	aca	gcc	tgg	agg	aag	atc	tgc	ccc	457
Gln	Tyr	Thr	Ser	Gln	Gly	Gly	Val	Thr	Ala	Trp	Arg	Lys	Ile	Cys	Pro	
94					99					104					109	
atc	ttt	gag	ggc	att	ggc	tat	gcc	tcc	cag	atg	atc	gtc	atc	ctc	ctc	505
Ile	Phe	Glu	Gly	Ile	Gly	Tyr	Ala	Ser	Gln	Met	Ile	Val	Ile	Leu	Leu	
110					115					120					125	
aac	gtc	tac	tac	atc	att	gtg	ttg	gcc	tgg	gcc	ctg	ttc	tac	ctc	ttc	553
Asn	Val	Tyr	Tyr	Ile	Ile	Val	Leu	Ala	Trp	Ala	Leu	Phe	Tyr	Leu	Phe	
126					131					136					141	
agc	agc	ttc	acc	atc	gac	ctg	ccc	tgg	ggc	ggc	tgc	tac	cat	gag	tgg	601
Ser	Ser	Phe	Thr	Ile	Asp	Leu	Pro	Trp	Gly	Gly	Cys	Tyr	His	Glu	Trp	
142					147					152					157	
aac	aca	gaa	cac	tgt	atg	gag	ttc	cag	aag	acc	aac	ggc	tcc	ctg	aat	649
Asn	Thr	Glu	His	Cys	Met	Glu	Phe	Gln	Lys	Thr	Asn	Gly	Ser	Leu	Asn	
158					163					168					173	
ggg	acc	tct	gag	aat	gcc	acc	tct	cct	gtc	atc	gag	ttc	tgg	gag	cgg	697
Gly	Thr	Ser	Glu	Asn	Ala	Thr	Ser	Pro	Val	Ile	Glu	Phe	Trp	Glu	Arg	
174					179					184					189	
cgg	gtc	ttg	aag	atc	tct	gat	ggg	atc	cag	cac	ctg	ggg	gcc	ctg	cgc	745
Arg	Val	Leu	Lys	Ile	Ser	Asp	Gly	Ile	Gln	His	Leu	Gly	Ala	Leu	Arg	
190					195					200					205	
tgg	gag	ctg	gct	ctg	tgc	ctc	ctg	ctg	gcc	tgg	gtc	atc	tgc	tac	ttc	793
Trp	Glu	Leu	Ala	Leu	Cys	Leu	Leu	Leu	Ala	Trp	Val	Ile	Cys	Tyr	Phe	
206					211					216					221	
tgc	atc	tgg	aag	ggg	gtg	aag	tcc	aca	ggc	aag	gtg	gtg	tac	ttc	acg	841
Cys	Ile	Trp	Lys	Gly	Val	Lys	Ser	Thr	Gly	Lys	Val	Val	Tyr	Phe	Thr	
222					227					232					237	



gcc aca ttt cct tac ctc atg ctg gtg gtc ctg tta att cga ggg gtg	889
Ala Thr Phe Pro Tyr Leu Met Leu Val Val Leu Leu Ile Arg Gly Val	
238 243 248 253	
acg ttg cct ggg gca gcc caa gga att cag ttt tac ctg tac cca aac	937
Thr Leu Pro Gly Ala Ala Gln Gly Ile Gln Phe Tyr Leu Tyr Pro Asn	
254 259 264 269	
ctc acg cgt ctg tgg gat ccc cag gtg tgg atg gat gca ggc acc cag	985
Leu Thr Arg Leu Trp Asp Pro Gln Val Trp Met Asp Ala Gly Thr Gln	
270 275 280 285	
ata ttc ttc tcc ttc gcc atc tgt ctt ggg tgc ctg aca gcc ctg ggc	1033
Ile Phe Phe Ser Phe Ala Ile Cys Leu Gly Cys Leu Thr Ala Leu Gly	
286 291 296 301	
agc tac aac aag tac cac aac aac tgc tac agc ggc acc agc ttt gtg	1081
Ser Tyr Asn Lys Tyr His Asn Asn Cys Tyr Ser Gly Thr Ser Phe Val	
302 307 312 317	
gcc ggc ttt gcc atc ttc tcc atc ctg ggc ttc atg tct cag gag cag	1129
Ala Gly Phe Ala Ile Phe Ser Ile Leu Gly Phe Met Ser Gln Glu Gln	
318 323 328 333	
ggg gtg ccc att tct gag gtg gcc gag tca ggc cct ggc ctg gct ttc	1177
Gly Val Pro Ile Ser Glu Val Ala Glu Ser Gly Pro Gly Leu Ala Phe	
334 339 344 349	
atc gct tac ccg cgg gct gtg gtg atg ctg ccc ttc tct cct ctc tgg	1225
Ile Ala Tyr Pro Arg Ala Val Val Met Leu Pro Phe Ser Pro Leu Trp	
350 355 360 365	
gcc tgc tgt ttc ttc ttc atg gtc gtt ctc ctg gga ctg gat agc cag	1273
Ala Cys Cys Phe Phe Phe Met Val Val Leu Leu Gly Leu Asp Ser Gln	
366 371 376 381	
ttt gtg tgt gta gaa agc ctg gtg aca gcg ctg gtg gac atg tac cct	1321
Phe Val Cys Val Glu Ser Leu Val Thr Ala Leu Val Asp Met Tyr Pro	
382 387 392 397	
cac gtg ttc cgc aag aag aac cgg agg gaa gtc ctc atc ctt gga gta	1369
His Val Phe Arg Lys Lys Asn Arg Arg Glu Val Leu Ile Leu Gly Val	
398 403 408 413	
tct gtc gtc tcc ttc cct gtg ggg ctg atc atg ctc aca gag ggc gga	1417
Ser Val Val Ser Phe Pro Val Gly Leu Ile Met Leu Thr Glu Gly Gly	
414 419 424 429	
atg tac gtg ttc cag ctc ttt gac tac tat gcg gcc agt ggc atg tgc	1465
Met Tyr Val Phe Gln Leu Phe Asp Tyr Tyr Ala Ala Ser Gly Met Cys	
430 435 440 445	
ctc ctg ttc gtg gcc atc ttc gag tcc ctc tgt gtg gct tgg gtt tac	1513
Leu Leu Phe Val Ala Ile Phe Glu Ser Leu Cys Val Ala Trp Val Tyr	
446 451 456 461	
gga gcc aag cgc ttc tac gac aac atc gaa gac atg att ggg tac agg	1561

Gly	Ala	Lys	Arg	Phe	Tyr	Asp	Asn	Ile	Glu	Asp	Met	Ile	Gly	Tyr	Arg	
462					467					472					477	
cca	tgg	cct	ctt	atc	aaa	tac	tgt	tgg	ctc	ttc	ctc	aca	cca	gct	gtg	1609
Pro	Trp	Pro	Leu	Ile	Lys	Tyr	Cys	Trp	Leu	Phe	Leu	Thr	Pro	Ala	Val	
478					483					488					493	
tgc	aca	gcc	acc	ttt	ctc	ttc	tcc	ctg	ata	aag	tac	act	ccg	ctg	acc	1657
Cys	Thr	Ala	Thr	Phe	Leu	Phe	Ser	Leu	Ile	Lys	Tyr	Thr	Pro	Leu	Thr	
494					499					504					509	
tac	aac	aag	aag	tac	acg	tac	ccg	tgg	tgg	ggc	gat	gcc	ctg	ggc	tgg	1705
Tyr	Asn	Lys	Lys	Tyr	Thr	Tyr	Pro	Trp	Trp	Gly	Asp	Ala	Leu	Gly	Trp	
510					515					520					525	
ctc	ctg	gct	ctg	tcc	tcc	tgg	tct	gca	ttc	ctg	cct	gga	gcc	tct	aca	1753
Leu	Leu	Ala	Leu	Ser	Ser	Trp	Ser	Ala	Phe	Leu	Pro	Gly	Ala	Ser	Thr	
526					531					536					541	
gac	tcg	gaa	ccc	tca	agg	gcc	cct	tca	gag	aga	gaa	tcc	gtc	agc	tca	1801
Asp	Ser	Glu	Pro	Ser	Arg	Ala	Pro	Ser	Glu	Arg	Glu	Ser	Val	Ser	Ser	
542					547					552					557	
tgt	gcc	cag	ccg	agg	acc	tgc	ccc	agc	gga	acc	cag	cag	gac	cct	cgg	1849
Cys	Ala	Gln	Pro	Arg	Thr	Cys	Pro	Ser	Gly	Thr	Gln	Gln	Asp	Pro	Arg	
558					563					568					573	
ctc	ccg	cca	ccc	cca	gga	cct	cac	tgc	tca	gac	tca	cag	agc	tag	agt	1897
Leu	Pro	Pro	Pro	Pro	Gly	Pro	His	Cys	Ser	Asp	Ser	Gln	Ser	*		
574					579					584						
ctcactgcta gggggcaggc ccttggatgg tgccctgtgtg cctggccttg gggatggctg															1957	
tggaggggaac gtggcagaag cagcccatg tggtccctgc ccccgacctg gagtggataa															2017	
gacaagaggg gtatttttga gtccacctgc tgagctggag gcctcccact gcaacttttc															2077	
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cttgaaggc															2146	

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 <212> DNA  
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<400> 78	
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	Met Ala Pro Leu Leu



gtgaactaag tccctataat aaaggctgag gctgcatctg ccaaaaaaaaa aaaa

930

<210> 79  
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<220>  
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<400> 79

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gcgtccg atg gcg gct gtg gtg ctg gcg gcg acg cgg ttg ctg cgg ggc 109  
Met Ala Ala Val Val Leu Ala Ala Thr Arg Leu Leu Arg Gly  
1 5 10

tcg ggt tct tgg ggc tgt tcg cgg ctg agg ttt gga cct cct gcg tat 157  
Ser Gly Ser Trp Gly Cys Ser Arg Leu Arg Phe Gly Pro Pro Ala Tyr  
15 20 25 30

aga cgg ttt agt agt ggt ggt gcc tat ccc aac atc ccc ctc tct tct 205  
Arg Arg Phe Ser Ser Gly Gly Ala Tyr Pro Asn Ile Pro Leu Ser Ser  
31 36 41 46

ccc tta cct gga gta ccc aag cct gtt ttt gct aca gtt gat gga cag 253  
Pro Leu Pro Gly Val Pro Lys Pro Val Phe Ala Thr Val Asp Gly Gln  
47 52 57 62

gaa aag ttt gaa acc aaa gta acc aca ttg gat aat ggg ctt cgc gtg 301  
Glu Lys Phe Glu Thr Lys Val Thr Thr Leu Asp Asn Gly Leu Arg Val  
63 68 73 78

gca tct cag aat aag ttt gga cag ttt tgt aca gta gga att ctt atc 349  
Ala Ser Gln Asn Lys Phe Gly Gln Phe Cys Thr Val Gly Ile Leu Ile  
79 84 89 94

aat tca gga tcg aga tat gaa gcg aaa tac ctt agt gga att gct cac 397  
Asn Ser Gly Ser Arg Tyr Glu Ala Lys Tyr Leu Ser Gly Ile Ala His  
95 100 105 110

ttt ttg gaa aaa ttg gca ttt tcg tct act gct cga ttt gac agc aaa 445  
Phe Leu Glu Lys Leu Ala Phe Ser Ser Thr Ala Arg Phe Asp Ser Lys  
111 116 121 126

gat gaa att ctg ctt acg ttg gaa aag cat ggg ggt atc tgt gac tgc 493  
Asp Glu Ile Leu Leu Thr Leu Glu Lys His Gly Gly Ile Cys Asp Cys  
127 132 137 142

cag aca tca aga gac acc acc atg tat gct gtg tct gct gat agc aaa 541  
Gln Thr Ser Arg Asp Thr Thr Met Tyr Ala Val Ser Ala Asp Ser Lys  
143 148 153 158

ggc ttg gac acg gtg gtt gcc tta ctg gct gat gtg gtt ctg cag ccc Gly Leu Asp Thr Val Val Ala Leu Leu Ala Asp Val Val Leu Gln Pro 159 164 169 174	589
cgg cta aca gat gaa gaa gtc gag atg acg cgg atg gcg gtc cag ttt Arg Leu Thr Asp Glu Glu Val Glu Met Thr Arg Met Ala Val Gln Phe 175 180 185 190	637
gag ctg gag gac ctg aac ctg cgg cct gac cca gag cca ctt ctc acc Glu Leu Glu Asp Leu Asn Leu Arg Pro Asp Pro Glu Pro Leu Leu Thr 191 196 201 206	685
gag atg att cat gaa gcg gct tac agg gag aac aca gtt ggc ctc cac Glu Met Ile His Glu Ala Ala Tyr Arg Glu Asn Thr Val Gly Leu His 207 212 217 222	733
cgt ttc tgc ccc aca gaa aac gta gca aag atc aat cga gag gtg ctg Arg Phe Cys Pro Thr Glu Asn Val Ala Lys Ile Asn Arg Glu Val Leu 223 228 233 238	781
cat tcc tac ctg agg aac tac tac act ccc gac cgc atg gtg ctg gcc His Ser Tyr Leu Arg Asn Tyr Tyr Thr Pro Asp Arg Met Val Leu Ala 239 244 249 254	829
ggc gtg ggc gtg gag cac gag cat ctg gtg gac tgt gcc cgg aag tac Gly Val Gly Val Glu His Glu His Leu Val Asp Cys Ala Arg Lys Tyr 255 260 265 270	877
ctc ctg ggg gtc cag ccg gcc tgg ggg agc gca gag gcc gtg gat att Leu Leu Gly Val Gln Pro Ala Trp Gly Ser Ala Glu Ala Val Asp Ile 271 276 281 286	925
gac aga tct gtg gcc cag tac act ggg ggg att gcc aag cta gaa aga Asp Arg Ser Val Ala Gln Tyr Thr Gly Gly Ile Ala Lys Leu Glu Arg 287 292 297 302	973
gac atg tcc aat gtc agc ctg ggc ccg acc ccc atc ccc gag ctc acg Asp Met Ser Asn Val Ser Leu Gly Pro Thr Pro Ile Pro Glu Leu Thr 303 308 313 318	1021
cac atc atg gtt gga ctg gag agc tgc tcc ttc ctg gag gag gac ttc His Ile Met Val Gly Leu Glu Ser Cys Ser Phe Leu Glu Glu Asp Phe 319 324 329 334	1069
atc ccc ttt gca gtg ttg aac atg atg atg ggc gga ggt ggc tcc ttc Ile Pro Phe Ala Val Leu Asn Met Met Met Gly Gly Gly Gly Ser Phe 335 340 345 350	1117
tcg gct ggt ggg ccc ggc aag ggc atg ttc tcc agg ctc tac ctc aac Ser Ala Gly Gly Pro Gly Lys Gly Met Phe Ser Arg Leu Tyr Leu Asn 351 356 361 366	1165
gtg ctc aac agg cac cac tgg atg tat aac gcg acc tcc tac cac cac Val Leu Asn Arg His His Trp Met Tyr Asn Ala Thr Ser Tyr His His 367 372 377 382	1213
agc tac gag gac act ggc ctc ctt tgc atc cat gcc agc gcc gac cca	1261

Ser	Tyr	Glu	Asp	Thr	Gly	Leu	Leu	Cys	Ile	His	Ala	Ser	Ala	Asp	Pro	
383					388					393					398	
aga	cag	gtt	cga	gaa	atg	gta	gaa	atc	atc	aca	aag	gag	ttt	att	tta	1309
Arg	Gln	Val	Arg	Glu	Met	Val	Glu	Ile	Ile	Thr	Lys	Glu	Phe	Ile	Leu	
399					404					409					414	
atg	ggc	gga	acc	gtg	gac	acg	gtg	gag	ctg	gaa	cga	gcc	aag	acg	cag	1357
Met	Gly	Gly	Thr	Val	Asp	Thr	Val	Glu	Leu	Glu	Arg	Ala	Lys	Thr	Gln	
415					420					425					430	
ctg	aca	tca	atg	ctc	atg	atg	aac	ctg	gaa	tcc	agg	cct	gtg	atc	ttc	1405
Leu	Thr	Ser	Met	Leu	Met	Met	Asn	Leu	Glu	Ser	Arg	Pro	Val	Ile	Phe	
431					436					441					446	
gag	gat	gtg	ggg	agg	cag	gtg	ctg	gcc	act	cgc	tcc	aga	aag	ctg	ccg	1453
Glu	Asp	Val	Gly	Arg	Gln	Val	Leu	Ala	Thr	Arg	Ser	Arg	Lys	Leu	Pro	
447					452					457					462	
cac	gag	ctg	tgc	acg	ctc	atc	cgc	aac	gtg	aag	ccg	gaa	gat	gtg	aag	1501
His	Glu	Leu	Cys	Thr	Leu	Ile	Arg	Asn	Val	Lys	Pro	Glu	Asp	Val	Lys	
463					468					473					478	
aga	gtc	gct	tct	aag	atg	ctc	cga	ggg	aag	ccg	gca	gtg	gcc	gcc	ctg	1549
Arg	Val	Ala	Ser	Lys	Met	Leu	Arg	Gly	Lys	Pro	Ala	Val	Ala	Ala	Leu	
479					484					489					494	
ggc	gac	ctg	act	gac	ctg	ccc	acg	tat	gag	cac	atc	cag	acc	gcc	ctg	1597
Gly	Asp	Leu	Thr	Asp	Leu	Pro	Thr	Tyr	Glu	His	Ile	Gln	Thr	Ala	Leu	
495					500					505					510	
tcg	agt	aag	gac	ggg	cgc	ctg	ccc	agg	acg	tac	cgg	ctc	ttc	cgg	tag	1645
Ser	Ser	Lys	Asp	Gly	Arg	Leu	Pro	Arg	Thr	Tyr	Arg	Leu	Phe	Arg	*	
511					516					521					526	
aaccgctccc cggcctgaca gacccagggg gctgcagctg gagcccgttc ccgtgcgtgt															1705	
tagtttggac acgaatttag tctaaaaagc tgtctggttg tataaacggt gcaaacaatg															1765	
tcgccacagc acccacgcgg tttgcattct tttggaactc aatgtgccga tcagtggagt															1825	
cagtatcgag cctgaccacc gcaagccagg aagcaggtga agtgcccagc gctggagtgc															1885	
agcgtgccac gaggagggcg gtcggtgctt ccctcctcgg gctgtgggca catggggccc															1945	
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cccggaggcc accgtgctgg gtaccaggac tcacctctga caagcaggag aaggtaagg															2065	
cccggtcagc tccaaggagc gcgctccacg cgcgtgcaca cagcttcctt ggtaataaag															2125	
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 <213> Homo sapiens

<220>  
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 <222> (1) .. (4080)

<400> 80

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1 5 10	
cgc ttg gcc cag agt gag cct tac aca acc atc cac cag cct ggc tac	96
Arg Leu Ala Gln Ser Glu Pro Tyr Thr Thr Ile His Gln Pro Gly Tyr	
17 22 27 32	
tgc gcc ttc tat gac gaa tgt ggg aag aac cca gag ctg tct gga agc	144
Cys Ala Phe Tyr Asp Glu Cys Gly Lys Asn Pro Glu Leu Ser Gly Ser	
33 38 43 48	
ctc atg aca ctc tcc aac gtg tcc tgc ctg tcc aac acg ccg gcc cgc	192
Leu Met Thr Leu Ser Asn Val Ser Cys Leu Ser Asn Thr Pro Ala Arg	
49 54 59 64	
aag atc aca ggt gat cac ctg atc cta tta cag aag atc tgc ccc cgc	240
Lys Ile Thr Gly Asp His Leu Ile Leu Leu Gln Lys Ile Cys Pro Arg	
65 70 75 80	
ctc tac acc ggc ccc aac acc caa gcc tgc tgc tcc gcc aag cag ctg	288
Leu Tyr Thr Gly Pro Asn Thr Gln Ala Cys Cys Ser Ala Lys Gln Leu	
81 86 91 96	
gta tca ctg gaa gcg agt ctg tcg atc acc aag gcc ctc ctc acc cgc	336
Val Ser Leu Glu Ala Ser Leu Ser Ile Thr Lys Ala Leu Leu Thr Arg	
97 102 107 112	
tgc cca gcc tgc tct gac aat ttt gtg aac ctg cac tgc cac aac acg	384
Cys Pro Ala Cys Ser Asp Asn Phe Val Asn Leu His Cys His Asn Thr	
113 118 123 128	
tgc agc ccc aat cag agc ctc ttc atc aat gtg acc cgc gtg gcc cag	432
Cys Ser Pro Asn Gln Ser Leu Phe Ile Asn Val Thr Arg Val Ala Gln	
129 134 139 144	
cta ggg gct gga caa ctc cca gct gtg gtg gcc tat gag gcc ttc tac	480
Leu Gly Ala Gly Gln Leu Pro Ala Val Val Ala Tyr Glu Ala Phe Tyr	
145 150 155 160	
cag cat agc ttt gcc gag cag agc tat gac tcc tgc agc cgt gtg cgc	528
Gln His Ser Phe Ala Glu Gln Ser Tyr Asp Ser Cys Ser Arg Val Arg	
161 166 171 176	
gtc cct gca gct gcc acg ctg gct gtg ggc acc atg tgt ggc gtg tat	576
Val Pro Ala Ala Ala Thr Leu Ala Val Gly Thr Met Cys Gly Val Tyr	
177 182 187 192	





Arg 417	Ser	Ser	Tyr	Arg	Tyr 422	Asp	Ser	Leu	Leu	Leu 427	Gly	Pro	Lys	Asn	Phe 432	
agc 433	gga	atc	ctg	gac	ctg 438	gac	ttg	ctg	ctg	gag 443	ctg	cta	gag	ctg	cag 448	1344
Ser	Gly	Ile	Leu	Asp	Leu	Asp	Leu	Leu	Leu	Glu	Leu	Leu	Glu	Leu	Gln	
gag 449	agg	ctg	cgg	cac	ctc 454	cag	gta	tgg	tcg	ccc 459	gaa	gca	cag	cgc	aac 464	1392
Glu	Arg	Leu	Arg	His	Leu	Gln	Val	Trp	Ser	Pro	Glu	Ala	Gln	Arg	Asn	
atc 465	tcc	ctg	cag	gac	atc 470	tgc	tac	gcc	ccc	ctc 475	aat	ccg	gac	aat	acc 480	1440
Ile	Ser	Leu	Gln	Asp	Ile	Cys	Tyr	Ala	Pro	Leu	Asn	Pro	Asp	Asn	Thr	
agt 481	ctc	tac	gac	tgc	tgc 486	atc	aac	agc	ctc	ctg 491	cag	tat	ttc	cag	aac 496	1488
Ser	Leu	Tyr	Asp	Cys	Cys	Ile	Asn	Ser	Leu	Leu	Gln	Tyr	Phe	Gln	Asn	
aac 497	cgc	acg	ctc	ctg	ctg 502	ctc	aca	gcc	aac	cag 507	aca	ctg	atg	ggg	cag 512	1536
Asn	Arg	Thr	Leu	Leu	Leu	Leu	Thr	Ala	Asn	Gln	Thr	Leu	Met	Gly	Gln	
acc 513	tcc	caa	gtc	gac	tgg 518	aag	gac	cat	ttt	ctg 523	tac	tgt	gcc	aat	gcc 528	1584
Thr	Ser	Gln	Val	Asp	Trp	Lys	Asp	His	Phe	Leu	Tyr	Cys	Ala	Asn	Ala	
ccg 529	ctc	acc	ttc	aag	gat 534	ggc	aca	gcc	ctg	gcc 539	ctg	agc	tgc	atg	gct 544	1632
Pro	Leu	Thr	Phe	Lys	Asp	Gly	Thr	Ala	Leu	Ala	Leu	Ser	Cys	Met	Ala	
gac 545	tac	ggg	gcc	cct	gtc 550	ttc	ccc	ttc	ctt	gcc 555	att	ggg	ggg	tac	aaa 560	1680
Asp	Tyr	Gly	Ala	Pro	Val	Phe	Pro	Phe	Leu	Ala	Ile	Gly	Gly	Tyr	Lys	
gga 561	aag	gac	tat	tct	gag 566	gca	gag	gcc	ctg	atc 571	atg	acg	ttc	tcc	ctc 576	1728
Gly	Lys	Asp	Tyr	Ser	Glu	Ala	Glu	Ala	Leu	Ile	Met	Thr	Phe	Ser	Leu	
aac 577	aat	tac	cct	gcc	ggg 582	gac	ccc	cgt	ctg	gcc 587	cag	gcc	aag	ctg	tgg 592	1776
Asn	Asn	Tyr	Pro	Ala	Gly	Asp	Pro	Arg	Leu	Ala	Gln	Ala	Lys	Leu	Trp	
gag 593	gag	gcc	ttc	tta	gag 598	gaa	atg	cga	gcc	ttc 603	cag	cgt	cgg	atg	gct 608	1824
Glu	Glu	Ala	Phe	Leu	Glu	Glu	Met	Arg	Ala	Phe	Gln	Arg	Arg	Met	Ala	
ggc 609	atg	ttc	cag	gtc	acg 614	ttc	atg	gct	gag	cgc 619	tct	ctg	gaa	gac	gag 624	1872
Gly	Met	Phe	Gln	Val	Thr	Phe	Met	Ala	Glu	Arg	Ser	Leu	Glu	Asp	Glu	
atc 625	aat	cgc	acc	aca	gct 630	gaa	gac	ctg	ccc	atc 635	ttt	gcc	acc	agc	tac 640	1920
Ile	Asn	Arg	Thr	Thr	Ala	Glu	Asp	Leu	Pro	Ile	Phe	Ala	Thr	Ser	Tyr	
att 641	gtc	ata	ttc	ctg	tac	atc	tct	ctg	gcc	ctg	ggc	agc	tat	tcc	agc 642	1968
Ile	Val	Ile	Phe	Leu	Tyr	Ile	Ser	Leu	Ala	Leu	Gly	Ser	Tyr	Ser	Ser	

641		646		651		656	
tgg agc cga gtg atg	gtg gac tcc aag gcc acg ctg ggc ctc ggc ggg		2016				
Trp Ser Arg Val Met	Val Asp Ser Lys Ala Thr Leu Gly Leu Gly Gly						
657	662	667	672				
gtg gcc gtg gtc ctg	gga gca gtc atg gct gcc atg ggc ttc ttc tcc		2064				
Val Ala Val Val Leu	Gly Ala Val Met Ala Ala Met Gly Phe Phe Ser						
673	678	683	688				
tac ttg ggt atc cgc	tcc tcc ctg gtc atc ctg caa gtg gtt cct ttc		2112				
Tyr Leu Gly Ile Arg	Ser Ser Leu Val Ile Leu Gln Val Val Pro Phe						
689	694	699	704				
ctg gtg ctg tcc gtg	ggg gct gat aac atc ttc atc ttt gtt ctc gag		2160				
Leu Val Leu Ser Val	Gly Ala Asp Asn Ile Phe Ile Phe Val Leu Glu						
705	710	715	720				
tac cag agg ctg ccc	cgg agg cct ggg gag cca cga gag gtc cac att		2208				
Tyr Gln Arg Leu Pro	Arg Arg Pro Gly Glu Pro Arg Glu Val His Ile						
721	726	731	736				
ggg cga gcc cta ggc	agg gtg gct ccc agc atg ctg ttg tgc agc ctc		2256				
Gly Arg Ala Leu Gly	Arg Val Ala Pro Ser Met Leu Leu Cys Ser Leu						
737	742	747	752				
tct gag gcc atc tgc	ttc ttc cta ggg gcc ctg acc ccc atg cca gct		2304				
Ser Glu Ala Ile Cys	Phe Phe Leu Gly Ala Leu Thr Pro Met Pro Ala						
753	758	763	768				
gtg cgg acc ttt gcc	ctg acc tct ggc ctt gca gtg atc ctt gac ttc		2352				
Val Arg Thr Phe Ala	Leu Thr Ser Gly Leu Ala Val Ile Leu Asp Phe						
769	774	779	784				
ctc ctg cag atg tca	gcc ttt gtg gcc ctg ctc tcc ctg gac agc aag		2400				
Leu Leu Gln Met Ser	Ala Phe Val Ala Leu Leu Ser Leu Asp Ser Lys						
785	790	795	800				
agg cag gag gcc tcc	cgg ttg gac gtc tgc tgc tgt gtc aag ccc cag		2448				
Arg Gln Glu Ala Ser	Arg Leu Asp Val Cys Cys Cys Val Lys Pro Gln						
801	806	811	816				
gag ctg ccc ccg cct	ggc cag gga gag ggg ctc ctg ctt ggc ttc ttc		2496				
Glu Leu Pro Pro Pro	Gly Gln Gly Glu Gly Leu Leu Leu Gly Phe Phe						
817	822	827	832				
caa aag gct tat gcc	ccc ttc ctg ctg cac tgg atc act cga ggt gtt		2544				
Gln Lys Ala Tyr Ala	Pro Phe Leu Leu His Trp Ile Thr Arg Gly Val						
833	838	843	848				
gtg ctg ctg ctg ttt	ctc gcc ctg ttc gga gtg agc ctc tac tcc atg		2592				
Val Leu Leu Leu Phe	Leu Ala Leu Phe Gly Val Ser Leu Tyr Ser Met						
849	854	859	864				
tgc cac atc agc gtg	gga ctg gac cag gag ctg gcc ctg ccc aag gac		2640				
Cys His Ile Ser Val	Gly Leu Asp Gln Glu Leu Ala Leu Pro Lys Asp						
865	870	875	880				









aag ggc acc agc ctc tct gac aag ctc agc ttc tcc acc cac acc ctc	1008
Lys Gly Thr Ser Leu Ser Asp Lys Leu Ser Phe Ser Thr His Thr Leu	
321 326 331 336	
ctt ggc cag ttc ttc cag ggc tgg ggc acg tgg gtg gct tcg tgg cct	1056
Leu Gly Gln Phe Phe Gln Gly Trp Gly Thr Trp Val Ala Ser Trp Pro	
337 342 347 352	
ctg acc atc ttg gtg cta tct gtc atc ccg gtg gtg gcc ttg gca gcg	1104
Leu Thr Ile Leu Val Leu Ser Val Ile Pro Val Val Ala Leu Ala Ala	
353 358 363 368	
ggc ctg gtc ttt aca gaa ctc act acg gac ccc gtg gag ctg tgg tcg	1152
Gly Leu Val Phe Thr Glu Leu Thr Thr Asp Pro Val Glu Leu Trp Ser	
369 374 379 384	
gcc ccc aac agc caa gcc cgg agt gag aaa gct ttc cat gac cag cat	1200
Ala Pro Asn Ser Gln Ala Arg Ser Glu Lys Ala Phe His Asp Gln His	
385 390 395 400	
ttc ggc ccc ttc ttc cga acc aac cag gtg atc ctg acg gct cct aac	1248
Phe Gly Pro Phe Phe Arg Thr Asn Gln Val Ile Leu Thr Ala Pro Asn	
401 406 411 416	
cgg tcc agc tac agg tat gac tct ctg ctg ctg ggg ccc aag aac ttc	1296
Arg Ser Ser Tyr Arg Tyr Asp Ser Leu Leu Leu Gly Pro Lys Asn Phe	
417 422 427 432	
agc gga atc ctg gac ctg gac ttg ctg ctg gag ctg cta gag ctg cag	1344
Ser Gly Ile Leu Asp Leu Asp Leu Leu Leu Glu Leu Leu Glu Leu Gln	
433 438 443 448	
gag agg ctg cgg cac ctc cag gta tgg tcg ccc gaa gca cag cgc aac	1392
Glu Arg Leu Arg His Leu Gln Val Trp Ser Pro Glu Ala Gln Arg Asn	
449 454 459 464	
atc tcc ctg cag gac atc tgc tac gcc ccc ctc aat ccg gac aat acc	1440
Ile Ser Leu Gln Asp Ile Cys Tyr Ala Pro Leu Asn Pro Asp Asn Thr	
465 470 475 480	
agt ctc tac gac tgc tgc atc aac agc ctc ctg cag tat ttc cag aac	1488
Ser Leu Tyr Asp Cys Cys Ile Asn Ser Leu Leu Gln Tyr Phe Gln Asn	
481 486 491 496	
aac cgc acg ctc ctg ctg ctc aca gcc aac cag aca ctg atg ggg cag	1536
Asn Arg Thr Leu Leu Leu Leu Thr Ala Asn Gln Thr Leu Met Gly Gln	
497 502 507 512	
acc tcc caa gtc gac tgg aag gac cat ttt ctg tac tgt gcc aat gcc	1584
Thr Ser Gln Val Asp Trp Lys Asp His Phe Leu Tyr Cys Ala Asn Ala	
513 518 523 528	
ccg ctc acc ttc aag gat ggc aca gcc ctg gcc ctg agc tgc atg gct	1632
Pro Leu Thr Phe Lys Asp Gly Thr Ala Leu Ala Leu Ser Cys Met Ala	
529 534 539 544	
gac tac ggg gcc cct gtc ttc ccc ttc ctt gcc att ggg ggg tac aaa	1680

Asp	Tyr	Gly	Ala	Pro	Val	Phe	Pro	Phe	Leu	Ala	Ile	Gly	Gly	Tyr	Lys	
545					550					555					560	
gga	aag	gac	tat	tct	gag	gca	gag	gcc	ctg	atc	atg	acg	ttc	tcc	ctc	1728
Gly	Lys	Asp	Tyr	Ser	Glu	Ala	Glu	Ala	Leu	Ile	Met	Thr	Phe	Ser	Leu	
561					566					571					576	
aac	aat	tac	cct	gcc	ggg	gac	ccc	cgt	ctg	gcc	cag	gcc	aag	ctg	tgg	1776
Asn	Asn	Tyr	Pro	Ala	Gly	Asp	Pro	Arg	Leu	Ala	Gln	Ala	Lys	Leu	Trp	
577					582					587					592	
gag	gag	gcc	ttc	tta	gag	gaa	atg	cga	gcc	ttc	cag	cgt	cgg	atg	gct	1824
Glu	Glu	Ala	Phe	Leu	Glu	Glu	Met	Arg	Ala	Phe	Gln	Arg	Arg	Met	Ala	
593					598					603					608	
ggc	atg	ttc	cag	gtc	acg	ttc	atg	gct	gag	cgc	tct	ctg	gaa	gac	gag	1872
Gly	Met	Phe	Gln	Val	Thr	Phe	Met	Ala	Glu	Arg	Ser	Leu	Glu	Asp	Glu	
609					614					619					624	
atc	aat	cgc	acc	aca	gct	gaa	gac	ctg	ccc	atc	ttt	gcc	acc	agc	tac	1920
Ile	Asn	Arg	Thr	Thr	Ala	Glu	Asp	Leu	Pro	Ile	Phe	Ala	Thr	Ser	Tyr	
625					630					635					640	
att	gtc	ata	ttc	ctg	tac	atc	tct	ctg	gcc	ctg	ggc	agc	tat	tcc	agc	1968
Ile	Val	Ile	Phe	Leu	Tyr	Ile	Ser	Leu	Ala	Leu	Gly	Ser	Tyr	Ser	Ser	
641					646					651					656	
tgg	agc	cga	gtg	atg	gtg	gac	tcc	aag	gcc	acg	ctg	ggc	ctc	ggc	ggg	2016
Trp	Ser	Arg	Val	Met	Val	Asp	Ser	Lys	Ala	Thr	Leu	Gly	Leu	Gly	Gly	
657					662					667					672	
gtg	gcc	gtg	gtc	ctg	gga	gca	gtc	atg	gct	gcc	atg	ggc	ttc	ttc	tcc	2064
Val	Ala	Val	Val	Leu	Gly	Ala	Val	Met	Ala	Ala	Met	Gly	Phe	Phe	Ser	
673					678					683					688	
tac	ttg	ggc	atc	cgc	tcc	tcc	ctg	gtc	atc	ctg	caa	gtg	gtt	cct	ttc	2112
Tyr	Leu	Gly	Ile	Arg	Ser	Ser	Leu	Val	Ile	Leu	Gln	Val	Val	Pro	Phe	
689					694					699					704	
ctg	gtg	ctg	tcc	gtg	ggg	gct	gat	aac	atc	ttc	atc	ttt	gtt	ctc	gag	2160
Leu	Val	Leu	Ser	Val	Gly	Ala	Asp	Asn	Ile	Phe	Ile	Phe	Val	Leu	Glu	
705					710					715					720	
tac	cag	agg	ctg	ccc	cgg	agg	cct	ggg	gag	cca	cga	gag	gtc	cac	att	2208
Tyr	Gln	Arg	Leu	Pro	Arg	Arg	Pro	Gly	Glu	Pro	Arg	Glu	Val	His	Ile	
721					726					731					736	
ggg	cga	gcc	cta	ggc	agg	gtg	gct	ccc	agc	atg	ctg	ttg	tgc	agc	ctc	2256
Gly	Arg	Ala	Leu	Gly	Arg	Val	Ala	Pro	Ser	Met	Leu	Leu	Cys	Ser	Leu	
737					742					747					752	
tct	gag	gcc	atc	tgc	ttc	ttc	cta	ggg	gcc	ctg	acc	ccc	atg	cca	gct	2304
Ser	Glu	Ala	Ile	Cys	Phe	Phe	Leu	Gly	Ala	Leu	Thr	Pro	Met	Pro	Ala	
753					758					763					768	
gtg	cgg	acc	ttt	gcc	ctg	acc	tct	ggc	ctt	gca	gtg	atc	ctt	gac	ttc	2352
Val	Arg	Thr	Phe	Ala	Leu	Thr	Ser	Gly	Leu	Ala	Val	Ile	Leu	Asp	Phe	









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gacccacgcg	tccgcccacg	cgctccggagc	cgtggaggta	cgaacttaag	acatgcctat	120
tttattaatt	tacttccaaa	cgcaacgaaa	ggtccatgga	caatttgtgg	gccatttaat	180
tcagggcccc	caattcgtac	gtggagaagt	gggaatgcaa	aagtactttg	acctttaacc	240
ttcgggtccgg	cgcggtggag	ggaaacgcct	ccgtctctat	ataaggaatt	ttccggtctc	300
ttcgggtcct	ttttcctctc	ttcagcgtgg	ggcgcccaca	atttgcgcgc	tctctttctg	360
ctgctcccca	gctctcggat	acagccgaca	cc	atg ggt ttc gga gac ctg aaa		413
				Met Gly Phe Gly Asp Leu Lys		
				1 5		
agc cct gcc ggc ctc cag gtg ctc aac gat tac ctg gcg gac aag agc	461					
Ser Pro Ala Gly Leu Gln Val Leu Asn Asp Tyr Leu Ala Asp Lys Ser						
8 13 18 23						
tac atc gag ggg tat gtg cca tca caa gca gat gtg gca gta ttt gaa	509					
Tyr Ile Glu Gly Tyr Val Pro Ser Gln Ala Asp Val Ala Val Phe Glu						
24 29 34 39						
gcc gtg tcc agc cca ccg cct gcc gac ttg tgt cat gcc cta cgt tgg	557					
Ala Val Ser Ser Pro Pro Pro Ala Asp Leu Cys His Ala Leu Arg Trp						
40 45 50 55						
tat aat cac atc aag tct tac gaa aag gaa aag gcc agc ctg cca gga	605					
Tyr Asn His Ile Lys Ser Tyr Glu Lys Glu Lys Ala Ser Leu Pro Gly						
56 61 66 71						
gtg aag aaa gct ttg ggc aaa tat ggt cct gcc gat gtg gaa gac act	653					
Val Lys Lys Ala Leu Gly Lys Tyr Gly Pro Ala Asp Val Glu Asp Thr						
72 77 82 87						
aca gga agt gga gct aca gat agt aaa gat gat gat gac att gac ctc	701					
Thr Gly Ser Gly Ala Thr Asp Ser Lys Asp Asp Asp Asp Ile Asp Leu						
88 93 98 103						
ttt gga tct gat gat gag gag gaa agt gaa gaa gca aag agg cta agg	749					
Phe Gly Ser Asp Asp Glu Glu Glu Ser Glu Glu Ala Lys Arg Leu Arg						
104 109 114 119						
gaa gaa cgt ctt gca caa tat gaa tca aag aaa gcc aaa aaa cct gca	797					
Glu Glu Arg Leu Ala Gln Tyr Glu Ser Lys Lys Ala Lys Lys Pro Ala						
120 125 130 135						
ctt gtt gcc aag tct tcc atc tta cta gat gtg aaa cct tgg gat gat	845					
Leu Val Ala Lys Ser Ser Ile Leu Leu Asp Val Lys Pro Trp Asp Asp						
136 141 146 151						
gag aca gat atg gcg aaa tta gag gag tgc gtc aga agc att caa gca	893					
Glu Thr Asp Met Ala Lys Leu Glu Glu Cys Val Arg Ser Ile Gln Ala						
152 157 162 167						

gac ggc tta gtc tgg ggc tca tct aaa cta gtt cca gtg gga tac gga	941
Asp Gly Leu Val Trp Gly Ser Ser Lys Leu Val Pro Val Gly Tyr Gly	
168 173 178 183	
att aag aaa ctt caa ata cag tgt gta gtt gaa gat gat aaa gtt gga	989
Ile Lys Lys Leu Gln Ile Gln Cys Val Val Glu Asp Asp Lys Val Gly	
184 189 194 199	
aca gat atg ctg gag gag cag atc act gct ttt gag gac tat gtg cag	1037
Thr Asp Met Leu Glu Glu Gln Ile Thr Ala Phe Glu Asp Tyr Val Gln	
200 205 210 215	
tcc atg gat gtg gct gct ttc aac aag atc taa aatccatc ctggatcatg	1088
Ser Met Asp Val Ala Ala Phe Asn Lys Ile *	
216 221 226	
gcattttaaat aaaagattga aagattaaaa aaaaaaaaa	1126

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 <212> DNA  
 <213> Homo sapiens

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 <221> CDS  
 <222> (86)..(2044)

<400> 83

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atagtcaaat taagaactct gtcac atg ata aat atg tgt ttt cag gaa ctc	112
Met Ile Asn Met Cys Phe Gln Glu Leu	
1 5	
gta aca ttc agg gat gtg gcc ata gaa ttc tcc cct gaa gag tgg aaa	160
Val Thr Phe Arg Asp Val Ala Ile Glu Phe Ser Pro Glu Glu Trp Lys	
10 15 20 25	
tgt ctg gac cct gcc cag cag aat ttg tat aga gat gtg atg ttg gag	208
Cys Leu Asp Pro Ala Gln Gln Asn Leu Tyr Arg Asp Val Met Leu Glu	
26 31 36 41	
aac tac agg aac ctg gtc tcc ctg ggt ttt gtg atc tct aac cca gac	256
Asn Tyr Arg Asn Leu Val Ser Leu Gly Phe Val Ile Ser Asn Pro Asp	
42 47 52 57	
ctg gtc acc tgt ctg gag caa ata aaa gag ccc tgc aat ttg aag ata	304
Leu Val Thr Cys Leu Glu Gln Ile Lys Glu Pro Cys Asn Leu Lys Ile	
58 63 68 73	
cat gag aca gca gcc aaa ccc cca gct ata tgt tct cct ttc agc caa	352
His Glu Thr Ala Ala Lys Pro Pro Ala Ile Cys Ser Pro Phe Ser Gln	
74 79 84 89	





538	543	548	553	
ctg aat gaa cat aag aaa att cat tct gga gag aaa ccc tac aaa tgc				1792
Leu Asn Glu His Lys Lys Ile His Ser Gly Glu Lys Pro Tyr Lys Cys				
554	559	564	569	
aaa gaa tgt ggc aaa gcc tat aac tta tcc tca acc ctt act aaa cat				1840
Lys Glu Cys Gly Lys Ala Tyr Asn Leu Ser Ser Thr Leu Thr Lys His				
570	575	580	585	
aag aga att cat act gga gag aaa ccc ttc aca tgt gaa gaa tgt ggc				1888
Lys Arg Ile His Thr Gly Glu Lys Pro Phe Thr Cys Glu Glu Cys Gly				
586	591	596	601	
aaa gcc ttc aat tgg tcc tca tcc ctt act aaa cat aag ata att cat				1936
Lys Ala Phe Asn Trp Ser Ser Ser Leu Thr Lys His Lys Ile Ile His				
602	607	612	617	
act gga gag aaa tcc tac aaa tgt gaa gaa tgt ggc aaa ggt ttt aat				1984
Thr Gly Glu Lys Ser Tyr Lys Cys Glu Glu Cys Gly Lys Gly Phe Asn				
618	623	628	633	
cgg ccc tca acc ctt act gta cac aag cga ttc ata ctg gca agg aac				2032
Arg Pro Ser Thr Leu Thr Val His Lys Arg Phe Ile Leu Ala Arg Asn				
634	639	644	649	
ata gtt gaa tga				2044
Ile Val Glu *				
650				

<210> 84  
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 <212> DNA  
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<400> 84

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	1 5	
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Phe Glu Asp Ile Ala Ile Tyr Phe Ser Gln Asp Glu Trp Gly Leu Leu		
10 15 20 25		
gat gag gct cag aga ctc ctg tac ctt gaa gtg atg ctg gag aac ttt		147
Asp Glu Ala Gln Arg Leu Leu Tyr Leu Glu Val Met Leu Glu Asn Phe		
26 31 36 41		
gcc ctt gta gcc tca ctg ggt tgt ggc cat gga aca gag gat gaa gag		195







<213> Homo sapiens

<220>

<221> CDS

<222> (253)..(618)

<400> 85

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atccagtagg ggaatcagat tgtggccaaa ggtagtgtat taactctaga aaaggagatt      120
atatctacag ttcctcaaac aatttttagat ttttcttttc aaggacagct agagaagata      180
atgacataat aactatttcc ttttttagga tctgaatcta aaaatggtga agcagacagt      240
tcagataaag aa      atg aaa cat ggg caa aaa tct ccc act gga aaa caa      288
                    Met Lys His Gly Gln Lys Ser Pro Thr Gly Lys Gln
                      1          5          10

aca agt cag cac tta aaa cga tta aaa aag tct ggt tta ggg cac ttg      336
Thr Ser Gln His Leu Lys Arg Leu Lys Lys Ser Gly Leu Gly His Leu
  13          18          23          28

aaa tgg acc aaa gct gag gac att gac ata gaa acc cca gga tct att      384
Lys Trp Thr Lys Ala Glu Asp Ile Asp Ile Glu Thr Pro Gly Ser Ile
  29          34          39          44

ctt gtc aac act aac ttg agg gca tta ata aat aaa cat acg ttt gct      432
Leu Val Asn Thr Asn Leu Arg Ala Leu Ile Asn Lys His Thr Phe Ala
  45          50          55          60

tcc tta cct cag cat ttt caa caa tac ctc ctg ctt ttg ctc cca gaa      480
Ser Leu Pro Gln His Phe Gln Gln Tyr Leu Leu Leu Leu Leu Pro Glu
  61          66          71          76

gtg gat agg cag atg gga agt gat gga att tta cgc ctc agt act tca      528
Val Asp Arg Gln Met Gly Ser Asp Gly Ile Leu Arg Leu Ser Thr Ser
  77          82          87          92

gct cta aat aat gaa ttc ttt gca tat gca gca caa ggg tgg aaa cag      576
Ala Leu Asn Asn Glu Phe Phe Ala Tyr Ala Ala Gln Gly Trp Lys Gln
  93          98          103          108

cga ctg gca gaa ggt aaa ttt gta ttt tct att att atg tga catattg      625
Arg Leu Ala Glu Gly Lys Phe Val Phe Ser Ile Ile Met *
  109          114          119

gagtacacat accgtactga gcttgtacct ttctctgatt tttcagtctt ttccccgaca      685
cagtacactt taatttagta aaaactcata tccctttcca aatgagttca ctgattcttt      745
tggtatactt gacattattg atgtcagata tttttgaaga aagcataatt ttatcttgga      805
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<210> 86  
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<220>  
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 <222> (99) .. (1976)

<400> 86

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atg cca ggc aca aaa	1
Met Pro Gly Thr Lys	
cgg ttt caa cat gtc att gag acc ccg gag cct ggc aag tgg gag ttg	161
Arg Phe Gln His Val Ile Glu Thr Pro Glu Pro Gly Lys Trp Glu Leu	
6 11 16 21	
tct ggg tac gag gca gct gtg cca atc acg gag aag tca aac cca ctg	209
Ser Gly Tyr Glu Ala Ala Val Pro Ile Thr Glu Lys Ser Asn Pro Leu	
22 27 32 37	
acc cag gat cta gac aaa gca gat gct gag aac att gtt cga ctg cta	257
Thr Gln Asp Leu Asp Lys Ala Asp Ala Glu Asn Ile Val Arg Leu Leu	
38 43 48 53	
ggg caa tgt gat gct gag atc ttc cag gag gag ggg caa gcc ctg tcc	305
Gly Gln Cys Asp Ala Glu Ile Phe Gln Glu Glu Gly Gln Ala Leu Ser	
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Thr Tyr Gln Arg Leu Tyr Ser Glu Ser Ile Leu Thr Thr Met Val Gln	
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Val Ala Gly Lys Val Gln Glu Val Leu Lys Glu Pro Asp Gly Gly Leu	
86 91 96 101	
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Val Val Leu Ser Gly Gly Gly Thr Ser Gly Arg Met Ala Phe Leu Met	
102 107 112 117	
tcg gtg tcc ttt aat cag ctg atg aaa ggt ctg gga cag aaa cct ctt	497
Ser Val Ser Phe Asn Gln Leu Met Lys Gly Leu Gly Gln Lys Pro Leu	
118 123 128 133	
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Tyr Thr Tyr Leu Ile Ala Gly Gly Asp Arg Ser Val Val Ala Ser Arg	
134 139 144 149	
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Glu Gly Thr Glu Asp Ser Ala Leu His Gly Ile Glu Glu Leu Lys Lys	
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Val Ala Ala Gly Lys Lys Arg Val Ile Val Ile Gly Ile Ser Val Gly	
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Leu Ser Ala Pro Phe Val Ala Gly Gln Met Asp Cys Cys Met Asn Asn	
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Thr Ala Val Phe Leu Pro Val Leu Val Gly Phe Asn Pro Val Ser Met	
198 203 208 213	
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Ala Arg Asn Asp Pro Ile Glu Asp Trp Ser Ser Thr Phe Arg Gln Val	
214 219 224 229	
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Ala Glu Arg Met Gln Lys Met Gln Glu Lys Gln Lys Ala Phe Val Leu	
230 235 240 245	
aat cct gcc atc ggg ccc gag ggt ctc agc ggc tcc tcc cgg atg aaa	881
Asn Pro Ala Ile Gly Pro Glu Gly Leu Ser Gly Ser Ser Arg Met Lys	
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Gly Gly Ser Ala Thr Lys Ile Leu Leu Glu Thr Leu Leu Leu Ala Ala	
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His Lys Thr Val Asp Gln Gly Ile Ala Ala Ser Gln Arg Cys Leu Leu	
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Glu Ile Leu Arg Thr Phe Glu Arg Ala His Gln Val Thr Tyr Ser Gln	
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Ser Pro Lys Ile Ala Thr Leu Met Lys Ser Val Ser Thr Ser Leu Glu	
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Lys Lys Gly His Val Tyr Leu Val Gly Trp Gln Thr Leu Gly Ile Ile	
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Ala Ile Met Asp Gly Val Glu Cys Ile His Thr Phe Gly Ala Asp Phe	
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Arg Asp Val Arg Gly Phe Leu Ile Gly Asp His Ser Asp Met Phe Asn	
358 363 368 373	
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Gln Lys Ala Glu Leu Thr Asn Gln Gly Pro Gln Phe Thr Phe Ser Gln	
374 379 384 389	
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Glu 390	Asp	Phe	Leu	Thr	Ser 395	Ile	Leu	Pro	Ser	Leu 400	Thr	Glu	Ile	Asp	Thr 405	
gtg 406	gtc	ttc	att	ttc	acc 411	ctg	gat	gac	aac	ctc 416	acg	gag	gtg	cag	act 421	1361
Val	Val	Phe	Ile	Phe	Thr	Leu	Asp	Asp	Asn	Leu	Thr	Glu	Val	Gln	Thr	
ata 422	gtg	gag	cag	gtg	aaa 427	gag	aag	acc	aac	cac 432	atc	cag	gcc	ctg	gca 437	1409
Ile	Val	Glu	Gln	Val	Lys	Glu	Lys	Thr	Asn	His	Ile	Gln	Ala	Leu	Ala	
cac 438	agc	acc	gtg	ggc	cag 443	acc	ttg	ctg	atc	cct 448	ctg	aag	aag	ctc	ttt 453	1457
His	Ser	Thr	Val	Gly	Gln	Thr	Leu	Leu	Ile	Pro	Leu	Lys	Lys	Leu	Phe	
ccc 454	tcc	atc	atc	agc	atc 459	aca	tgg	cca	ctg	ctt 464	ttc	ttt	gaa	tat	gaa 469	1505
Pro	Ser	Ile	Ile	Ser	Ile	Thr	Trp	Pro	Leu	Leu	Phe	Phe	Glu	Tyr	Glu	
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Gly	Asn	Phe	Ile	Gln	Lys	Phe	Gln	Arg	Glu	Leu	Ser	Thr	Lys	Trp	Val	
ctg 486	aat	aca	gtg	agt	aca 491	ggc	gct	cat	gtg	ctt 496	ctt	ggc	aag	atc	cta 501	1601
Leu	Asn	Thr	Val	Ser	Thr	Gly	Ala	His	Val	Leu	Leu	Gly	Lys	Ile	Leu	
caa 502	aac	cac	atg	ttg	gac 507	ctt	cgg	att	agc	aac 512	tcc	aag	ctc	ttc	tgg 517	1649
Gln	Asn	His	Met	Leu	Asp	Leu	Arg	Ile	Ser	Asn	Ser	Lys	Leu	Phe	Trp	
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Arg	Ala	Leu	Ala	Met	Leu	Gln	Arg	Phe	Ser	Gly	Gln	Ser	Lys	Ala	Arg	
tgc 534	atc	gag	agc	ctc	ctc 539	cga	gcg	atc	cac	ttt 544	ccc	cag	cca	ctg	tca 549	1745
Cys	Ile	Glu	Ser	Leu	Leu	Arg	Ala	Ile	His	Phe	Pro	Gln	Pro	Leu	Ser	
gat 550	gat	att	cgg	gct	gct 555	ccc	atc	tcc	tgc	cgt 560	gtc	cag	gtt	gca	cat 565	1793
Asp	Asp	Ile	Arg	Ala	Ala	Pro	Ile	Ser	Cys	Arg	Val	Gln	Val	Ala	His	
gag 566	aag	gaa	cag	gtg	ata 571	ccc	atc	gcc	ttg	ctg 576	agc	ctc	cta	ttc	cgg 581	1841
Glu	Lys	Glu	Gln	Val	Ile	Pro	Ile	Ala	Leu	Leu	Ser	Leu	Leu	Phe	Arg	
tgc 582	tcg	atc	act	gag	gct 587	cag	gca	cac	ctg	gct 592	gca	gct	cct	tct	gtc 597	1889
Cys	Ser	Ile	Thr	Glu	Ala	Gln	Ala	His	Leu	Ala	Ala	Ala	Pro	Ser	Val	
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Cys	Glu	Ala	Val	Arg	Ser	Ala	Leu	Ala	Gly	Pro	Gly	Gln	Lys	Arg	Thr	
gcg 614	gac	ccc	ctc	gag	atc	cta	gag	cct	gac	gtt	cag	tga	acccatg	gttt		1986
Ala	Asp	Pro	Leu	Glu	Ile	Leu	Glu	Pro	Asp	Val	Gln	*				







Ser Asn Pro Ala Gln Val Asp Leu Gly Ala Ala Thr Ala Glu Gly Gly	
332 337 342 347	
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Ala Pro Glu Ala Ile Ser Gly Val Pro Thr Pro Pro Ala Ile Pro Pro	
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Gln Pro Arg Pro Arg Ser Leu Ala Ser Glu Thr Asn *	
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gagccaccgg aaggaaggag aggtttgcct gctcctacgg gactgattct tctcttgccg	1574
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gccgggcagg ggctccttg aagggaacct cctgcagcct caagcaccag gtcattgac	178
atg aca tct atc cct ttc cca ggt gac cga ctc ctg cag gtg gat gga	226
Met Thr Ser Ile Pro Phe Pro Gly Asp Arg Leu Leu Gln Val Asp Gly	
1 5 10 15	
gtg att ctg tgc ggc ctc acc cac aag cag gct gtg cag tgc ctg aag	274
Val Ile Leu Cys Gly Leu Thr His Lys Gln Ala Val Gln Cys Leu Lys	
17 22 27 32	
ggc cct ggg cag gtt gca aga ctg gtc tta gag aga aga gtc ccc agg	322
Gly Pro Gly Gln Val Ala Arg Leu Val Leu Glu Arg Arg Val Pro Arg	
33 38 43 48	
agt aca cag cag tgt cct tct gct aat gac agc atg gga gat gaa cgc	370
Ser Thr Gln Gln Cys Pro Ser Ala Asn Asp Ser Met Gly Asp Glu Arg	
49 54 59 64	



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Asp Val Arg Gln Asn Cys Tyr Ser Val Cys Asp Ile Met Arg Leu Gly
289                               294                   299           304

aga tat tcc ttc tca tct cct cta acc aga ctt tcg aca gat att ttc      1138
Arg Tyr Ser Phe Ser Ser Pro Leu Thr Arg Leu Ser Thr Asp Ile Phe
305                               310                   315           320

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ttcagctggc tcatccccag gggctggggg ctcttgata caatggagca gatgagccgg      180
gaggacatgc tggccatctc aacacccgctc ttgaccagtc tggatgtgcc ccctgagatg      240
atgcccaccg tcatagatga atacctagga agcaactcgg acgcacaagc caaatgccag      300
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taccttcgag attctggaag ccctgtcttt ttctatgagt tccagcatcg acccagttct      420
tttgcaaga tcaaacctgc ctgggtgaag gctgatcatg gggccgaggg tgcttttgtg      480
ttcggaggtc ccttcctcat ggacgagagc tcccgcttgg cctttccaga ggccacagag      540
gaggagaagc agctaagcct caccatgatg gccagtgga ccactttgc ccggacagga      600
cctcccacac tttggggcat cgttgccact ggagcctctc ttcgggtgac gttgcccctc      660
cctgctgccc ccaagctggc cccttcccac tcttcagacc ttgaccagga ccccaggaaa      720
caaggcaatc gctggcggtg cgggcctctg ggccgtcctc tggggttccg agaggacccc      780
accttacaga tgaggaaatt agaatacagag aggggcagta ccgtgcctga ggccacacag      840
gctgaggccc caggataagt tccttgtgct ggcctcagat ggctgtggg ac      atg      895
                                     Met
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ctg agc aat gag gac gtg gta agg ctg gtg gtg ggg cac ctg gct gag	943
Leu Ser Asn Glu Asp Val Val Arg Leu Val Val Gly His Leu Ala Glu	
2 7 12 17	
gca gat tgg cac aag aca gac ctg gcc cag aga ccc gcc aac ttg ggg	991
Ala Asp Trp His Lys Thr Asp Leu Ala Gln Arg Pro Ala Asn Leu Gly	
18 23 28 33	
ctc atg cag agc ctg ctg ctg cag agg aaa gcc agc ggg ctc cac gag	1039
Leu Met Gln Ser Leu Leu Leu Gln Arg Lys Ala Ser Gly Leu His Glu	
34 39 44 49	
gct gac caa aat gca gcc acg cgg ctg atc aga cat gcc atc ggg aac	1087
Ala Asp Gln Asn Ala Ala Thr Arg Leu Ile Arg His Ala Ile Gly Asn	
50 55 60 65	
aat gag tat ggg gag atg gag gca gag cgg ctg gcg gcg atg ctg aca	1135
Asn Glu Tyr Gly Glu Met Glu Ala Glu Arg Leu Ala Ala Met Leu Thr	
66 71 76 81	
ttg cca gag gac ttg gcg agg atg tac agg gat gat atc act gtc act	1183
Leu Pro Glu Asp Leu Ala Arg Met Tyr Arg Asp Asp Ile Thr Val Thr	
82 87 92 97	
gtg gtg tat ttt aac tca gaa tca atc ggt gca tat tac aag ggg ggt	1231
Val Val Tyr Phe Asn Ser Glu Ser Ile Gly Ala Tyr Tyr Lys Gly Gly	
98 103 108 113	
taa gaat ctcccatcct attgtcaagg ttaacataaa tgctcttcta aaatgtttca	1288
* 114	
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gccgacaggc atcccctgag cgctgctgg gctcttatca cgcg atg gca tcc act	176
Met Ala Ser Thr	

1







ata gga agt ctg aaa tcg aag ctc tag tggga ctggcacatt cagccaagtc 2292  
 Ile Gly Ser Leu Lys Ser Lys Leu \*  
 693 698  
 taatgaaacg aaggggaacta atcagacgtg gacctcaact tctgattcca gaacacgccg 2352  
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 ttgcagcgtg gaaaagaaat gcagatgac atgtctacct gatgcgccgt gggttttttg 2532  
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 cccattgtca gggaaaaa 2610

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 atg gaa cgt gta ggt tgt act tta acg aca act tac gcc cac cct aga 224  
 Met Glu Arg Val Gly Cys Thr Leu Thr Thr Thr Tyr Ala His Pro Arg  
 1 5 10 15  
 cca aca cca acc aac ttt cta cca gcc atc agt acc atg gcc tca agc 272  
 Pro Thr Pro Thr Asn Phe Leu Pro Ala Ile Ser Thr Met Ala Ser Ser  
 17 22 27 32  
 tac agg gac cgc ttt ccc cac tcc aat ttg acc cat agc ctg agc ctt 320  
 Tyr Arg Asp Arg Phe Pro His Ser Asn Leu Thr His Ser Leu Ser Leu  
 33 38 43 48  
 cct tgg aga ccc agc aca tac tac aaa gtc gcc tcc aat tcc cca agc 368  
 Pro Trp Arg Pro Ser Thr Tyr Tyr Lys Val Ala Ser Asn Ser Pro Ser  
 49 54 59 64  
 gtg gcc ccg tac tgc acc aga tca cag agg gtg tcc gag aat acc atg 416  
 Val Ala Pro Tyr Cys Thr Arg Ser Gln Arg Val Ser Glu Asn Thr Met  
 65 70 75 80  
 ctt ccc ttt gtt tcc aac aga acc act ttc ttc aca aga tac aca ccg 464  
 Leu Pro Phe Val Ser Asn Arg Thr Thr Phe Phe Thr Arg Tyr Thr Pro







Thr	Leu	Glu	Glu	Phe	Lys	Glu	Ala	Ala	Lys	Ser	Asp	Pro	Ser	Ile	Val	
167					172					177					182	
ttg ctg ctg cag tgt gac atg cag aag tag a agctgggtgag gggcagggtc 993 Leu Leu Leu Gln Cys Asp Met Gln Lys * 183 188																
cctggccaga aggggcatgg ccacctccca acctgatgac ctctctggct ggcctcccag 1053																
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atg gcc aag tgg ggt gag gga gac cca cgc tgg atc gtg gag gag cgg 164															
Met	Ala	Lys	Trp	Gly	Glu	Gly	Asp	Pro	Arg	Trp	Ile	Val	Glu	Glu	Arg
1				5				10					15		
gcg gac gcc acc aac gtc aac aac tgg cac tgg acg gag aga gat gct 212															
Ala	Asp	Ala	Thr	Asn	Val	Asn	Asn	Trp	His	Trp	Thr	Glu	Arg	Asp	Ala
17				22				27					32		
tca aat tgg tcc acg gat aag ctg aaa aca ctg ttc ttg gca gtg cag 260															
Ser	Asn	Trp	Ser	Thr	Asp	Lys	Leu	Lys	Thr	Leu	Phe	Leu	Ala	Val	Gln
33				38				43					48		





Thr 65	Phe	Thr	Arg	Ala	Gln 70	Leu	Asp	Val	Leu	Glu 75	Ala	Leu	Phe	Ala	Lys 80	
acc Thr 81	cgg Arg	tac Tyr	cca Pro	gac Asp	atc Ile 86	ttc Phe	atg Met	cga Arg	gag Glu	gag Glu 91	gtg Val	gca Ala	ctg Leu	aaa Lys	atc Ile 96	288
aac Asn 97	ttg Leu	ccc Pro	gag Glu	tcg Ser	agg Arg 102	gtg Val	cag Gln	gta Val	tgg Trp	ttt Phe 107	aag Lys	aat Asn	cga Arg	aga Arg	gct Ala 112	336
aag Lys 113	tgc Cys	cgc Arg	caa Gln	caa Gln	cag Gln 118	caa Gln	caa Gln	cag Gln	cag Gln	aat Asn 123	gga Gly	ggt Gly	caa Gln	aac Asn	aaa Lys 128	384
gtg Val 129	aga Arg	cct Pro	gcc Ala	aaa Lys	aag Lys 134	aag Lys	aca Thr	tct Ser	cca Pro	gct Ala 139	cgg Arg	gaa Glu	gtg Val	agt Ser	tca Ser 144	432
gag Glu 145	agt Ser	gga Gly	aca Thr	agt Ser	ggc Gly 150	caa Gln	ttc Phe	act Thr	ccc Pro	ccc Pro 155	tct Ser	agc Ser	acc Thr	tca Ser	gtc Val 160	480
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tcc Ser 177	atc Ile	tcc Ser	cca Pro	ctg Leu	tca Ser 182	gat Asp	ccc Pro	ttg Leu	tcc Ser	acc Thr 187	tcc Ser	tct Ser	tcc Ser	tgc Cys	atg Met 192	576
cag Gln 193	agg Arg	tcc Ser	tat Tyr	ccc Pro	atg Met 198	acc Thr	tat Tyr	act Thr	cag Gln	gct Ala 203	tca Ser	ggt Gly	tat Tyr	agt Ser	caa Gln 208	624
gga Gly 209	tat Tyr	gct Ala	ggc Gly	tca Ser	act Thr 214	tcc Ser	tac Tyr	ttt Phe	ggg Gly	ggc Gly 219	atg Met	gac Asp	tgt Cys	gga Gly	tca Ser 224	672
tat Tyr 225	ttg Leu	acc Thr	cct Pro	atg Met	cat His 230	cac His	cag Gln	ctt Leu	ccc Pro	gga Gly 235	cca Pro	ggg Gly	gcc Ala	aca Thr	ctc Leu 240	720
agt Ser 241	ccc Pro	atg Met	ggt Gly	acc Thr	aat Asn 246	gca Ala	gtc Val	acc Thr	agc Ser	cat His 251	ctc Leu	aat Asn	cag Gln	tcc Ser	cca Pro 256	768
gct Ala 257	tct Ser	ctt Leu	tcc Ser	acc Thr	cag Gln 262	gga Gly	tat Tyr	gga Gly	gct Ala	tca Ser 267	agc Ser	ttg Leu	ggt Gly	ttt Phe	aac Asn 272	816
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ctt Leu	aac Asn	ttc Phe	aat Asn	gct Ala	gac Asp	tgc Cys	ttg Leu	gat Asp	tat Tyr	aaa Lys	gat Asp	cag Gln	aca Thr	tcc Ser	tcg Ser	912

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	Met Ala Gln Arg Asp Trp Thr			
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Trp Val Pro Ser Gly Ala Ala Ala Met Gly Leu Gly Val Ser Ala Glu				
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cag ccc gca ggc ggc gcc gag ggc ttc cac ctg cac ggg gtg cag gag				209
Gln Pro Ala Gly Gly Ala Glu Gly Phe His Leu His Gly Val Gln Glu				
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Asn Ser Pro Ala Gln Gln Ala Gly Leu Glu Pro Tyr Phe Asp Phe Ile				
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Ile Thr Ile Gly His Ser Arg Leu Asn Lys Glu Asn Asp Thr Leu Lys				
56 61 66 71				
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Ala Leu Leu Lys Ala Asn Val Glu Lys Pro Val Lys Leu Glu Val Phe				
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Asn Met Lys Thr Met Arg Val Arg Glu Val Glu Val Val Pro Ser Asn				
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Phe Arg Arg Ala Ser Glu Gln Val Trp His Val Leu Asp Val Glu Pro	
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Ser Ser Pro Ala Ala Leu Ala Gly Leu Arg Pro Tyr Thr Asp Tyr Val	
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Val Gly Ser Asp Gln Ile Leu Gln Glu Ser Glu Asp Phe Phe Thr Leu	
152 157 162 167	
atc gag tct cat gag ggg aag ccc ttg aag ctg atg gtg tat aac tcc	641
Ile Glu Ser His Glu Gly Lys Pro Leu Lys Leu Met Val Tyr Asn Ser	
168 173 178 183	
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Lys Ser Asp Ser Cys Arg Glu Val Thr Val Thr Pro Asn Ala Ala Trp	
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Gly Gly Glu Gly Ser Leu Gly Cys Gly Ile Gly Tyr Gly Tyr Leu His	
200 205 210 215	
cgg atc cca act cag ccc ccc agc tac cac aag aag cca cct ggc acc	785
Arg Ile Pro Thr Gln Pro Pro Ser Tyr His Lys Lys Pro Pro Gly Thr	
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cca cca cct tct gct cta cca ctt ggt gcc cca cca cct gat gct cta	833
Pro Pro Pro Ser Ala Leu Pro Leu Gly Ala Pro Pro Pro Asp Ala Leu	
232 237 242 247	
cca cct gga ccc acc ccc gag gac tct cct tcc ctg gag aca ggt tcc	881
Pro Pro Gly Pro Thr Pro Glu Asp Ser Pro Ser Leu Glu Thr Gly Ser	
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Arg Gln Ser Asp Tyr Met Glu Ala Leu Leu Gln Ala Pro Gly Ser Ser	
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Met Glu Asp Pro Leu Pro Gly Pro Gly Ser Pro Ser His Ser Ala Pro	
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Asp Pro Asp Gly Leu Pro His Phe Met Glu Thr Pro Leu Gln Pro Pro	
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Pro Pro Val Gln Arg Val Met Asp Pro Gly Phe Leu Asp Val Ser Gly	
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Ile Ser Leu Leu Asp Asn Ser Asn Ala Ser Val Trp Pro Ser Leu Pro	
328 333 338 343	
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Met Arg Leu Lys Arg Leu Gln Ile Glu Glu Ser Ser Lys Pro Val Arg				
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cta tca caa cag ctg gac aaa gtt gta aca acc aat tac aaa cct gtt				662
Leu Ser Gln Gln Leu Asp Lys Val Val Thr Thr Asn Tyr Lys Pro Val				
141	146	151	156	
gct aat cat caa tac aat atc gaa tat gaa agg aaa aag aaa gaa gac				710
Ala Asn His Gln Tyr Asn Ile Glu Tyr Glu Arg Lys Lys Lys Glu Asp				
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gga aag cga gct cga gct gat aaa caa cat gtt tta gac atg cta ttt				758
Gly Lys Arg Ala Arg Ala Asp Lys Gln His Val Leu Asp Met Leu Phe				
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tca gcc ttt gag aaa cat caa tac tat aat ctt aag gac ttg gtg gac				806
Ser Ala Phe Glu Lys His Gln Tyr Tyr Asn Leu Lys Asp Leu Val Asp				
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atc aca aaa caa cct gtg gtg tac ctg aag gaa atc tta aaa gaa att				854
Ile Thr Lys Gln Pro Val Val Tyr Leu Lys Glu Ile Leu Lys Glu Ile				
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Gly Val Gln Asn Val Lys Gly Ile His Lys Asn Thr Trp Glu Leu Lys				
221	226	231	236	
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Pro Glu Tyr Arg His Tyr Gln Gly Glu Glu Lys Ser Asp *				
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cctattttac      atg ctt aac cac atc ata agg ttg cag gca gta ctt gaa      228
                  Met Leu Asn His Ile Ile Arg Leu Gln Ala Val Leu Glu
                   1             5             10

atc atc atg aat gaa aga gca aat gca tta gat tta ctg gcc cag caa      276
Ile Ile Met Asn Glu Arg Ala Asn Ala Leu Asp Leu Leu Ala Gln Gln
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acc aca aaa atg aga aat gct aac tat cag aac aga tta gct tta gat      324
Thr Thr Lys Met Arg Asn Ala Asn Tyr Gln Asn Arg Leu Ala Leu Asp
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tac ctc cta gcc cac gaa gga gga gta tga g gaaagttcag tctaactaat      375
Tyr Leu Leu Ala His Glu Gly Gly Val *
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His	Gly	Lys	Val	Val	Ser	Ser	Gln	Asp	Pro	Arg	Thr	Lys	Ala	Gly	Leu	
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Tyr	Trp	Gly	Tyr	Thr	Val	Arg	Leu	Ala	Ser	Cys	Leu	Ser	Ala	Val	Phe	
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Ala	Glu	Ala	Pro	Phe	Gln	Asp	Gly	Tyr	Asp	Leu	Thr	Ile	Gly	Thr	Ser	
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Glu	Arg	Gly	Ser	Asp	Val	Ala	Ser	Ala	Gln	Leu	Pro	Asn	Phe	Arg	His	
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Ala	Leu	Val	Val	Phe	Gly	Gly	Leu	Gln	Gly	Leu	Glu	Ala	Gly	Ala	Asp	
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gct	gac	ccc	aac	ctg	gag	gtg	gct	gaa	ccc	agt	gtc	ctc	ttt	gac	ctg	1063
Ala	Asp	Pro	Asn	Leu	Glu	Val	Ala	Glu	Pro	Ser	Val	Leu	Phe	Asp	Leu	
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Tyr	Val	Asn	Thr	Cys	Pro	Gly	Gln	Gly	Ser	Arg	Thr	Ile	Arg	Thr	Glu	
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gaa	gcc	atc	ctc	atc	tcc	ctg	gcc	gcc	ctg	cag	cct	ggc	ctc	acc	cag	1159
Glu	Ala	Ile	Leu	Ile	Ser	Leu	Ala	Ala	Leu	Gln	Pro	Gly	Leu	Thr	Gln	
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Ser Lys Val Asn Arg Gly Trp Asn Ser Gly Arg Cys Lys Gln Arg Gly	
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Lys Thr Glu Gln Pro Gly Glu Pro Leu Glu His Val Tyr Val Thr Ile	
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Lys His Ala Val Ala Leu Glu Ser Arg His Gln Lys Gly Glu Leu Gln	
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Cys Leu Ile Lys Met Cys Ile Pro Leu Ser Lys Pro Leu Gln Met Phe	
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Ala Lys Asn Thr Arg Tyr Phe Arg Gln Arg Leu Gln Glu Met Gly Phe	
194 199 204 209	
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Ile Ile Tyr Gly Asn Glu Asn Ala Ser Val Val Pro Leu Leu Leu Tyr	
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Met Pro Gly Lys Val Ala Ala Phe Ala Arg His Met Leu Glu Lys Lys	
226 231 236 241	

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Ile Gly Val Val Val	Val Gly Phe Pro Ala Thr Pro Leu Ala Glu Ala	
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cgg gct cgg ttt tgt	gtt tca gcg gca cat acc cgg gag atg tta gac	1112
Arg Ala Arg Phe Cys	Val Ser Ala Ala His Thr Arg Glu Met Leu Asp	
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acg gtt tta gaa gct	ctt gat gaa atg ggt gat ctc ttg caa ctg aaa	1160
Thr Val Leu Glu Ala	Leu Asp Glu Met Gly Asp Leu Leu Gln Leu Lys	
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Tyr Ser Arg His Lys	Lys Ser Ala Arg Pro Glu Leu Tyr Asp Glu Thr	
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Ser Phe Glu Leu Glu	Asp *	
306	311	

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Phe Tyr Leu Glu Asn Gly Phe Gly Arg Ala Asp Ser Phe Pro Phe Ser	
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Val Glu Gln Ser Asn Leu Val Phe Asn Ile Gln Pro Ala Pro Ala Met	
56 61 66 71	
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Val Tyr Asp Tyr Tyr Glu Lys Glu Glu Tyr Ala Leu Ala Phe Tyr Asn	
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Ile Asp Ser Ser Ser Val Ser Glu *	
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Ser Asp Ser Cys Phe Arg Asn Leu Ala Glu Asp Arg Ser Gly Ile Asn	



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Leu	Ser	Thr	Thr	Pro	Ser	Glu	Ser	Pro	Arg	Ala	Gln	Ala	Thr	Ser	Arg	
263					268					273					278	
ctc	tct	aca	gct	tcc	tgc	cca	aca	cca	aaa	gtc	cag	tcc	agg	tgc	agc	978
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                1          5          10

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78          83          88          93

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Phe Glu Glu Ile Leu Asn Met Glu Pro Tyr Cys Cys Arg Glu Thr Leu
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Lys Ser Leu Arg Pro Glu Cys Phe Ile Tyr Asp Leu Ser Ala Val Val
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Met His His Gly Lys Gly Phe Gly Ser Gly His Tyr Thr Ala Tyr Cys
 97             102            107            112

tat aat tct gaa gga ggg ttc tgg gta cac tgc aat gat tcc aaa cta      740
Tyr Asn Ser Glu Gly Gly Phe Trp Val His Cys Asn Asp Ser Lys Leu
113             118            123            128

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Met Pro Pro Pro Gln Lys Ile Pro Ser Val Arg Pro Phe Lys Gln Arg	
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Lys Ser Leu Ala Ile Arg Gln Glu Glu Val Ala Gly Ile Arg Ala Lys	
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Thr Met Thr Gln Phe Leu Ser Ile Ile Arg Ser Arg Met Val Leu Arg	
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97 102 107 112	



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 60 65 70 75

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Met Leu Glu Gln Ile Arg Asn  
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Val Lys Pro Ser Ser Ser Lys Glu Leu Pro Ser Asp Phe Gln Leu *	
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cttgcttggtg gaatgtcagc tgcgtgagct cactgtcaga caag atg gaa gaa gaa      476
                                   Met Glu Glu Glu
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ggg ctg gag tgt cca aac tct tcc tct gaa aaa cgc tat ttt cct gaa      524
Gly Leu Glu Cys Pro Asn Ser Ser Ser Glu Lys Arg Tyr Phe Pro Glu
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tcc ctg gat tcc agc gat ggg gat gag gaa gag gtt ttg gcc tgt gag      572
Ser Leu Asp Ser Ser Asp Gly Asp Glu Glu Glu Val Leu Ala Cys Glu
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gat ttg gaa ctt aac ccc ttt gat gga ttg cca tat tca tca cgt tat      620
Asp Leu Glu Leu Asn Pro Phe Asp Gly Leu Pro Tyr Ser Ser Arg Tyr
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tat aaa ctt ctg aaa gaa aga gaa gat ctt cct ata tgg aaa gaa aaa      668
Tyr Lys Leu Leu Lys Glu Arg Glu Asp Leu Pro Ile Trp Lys Glu Lys
  53                               58                               63                               68

tac tcc ttt atg gag aac ctg ctt caa aat caa atc gtg att gtt tca      716
Tyr Ser Phe Met Glu Asn Leu Leu Gln Asn Gln Ile Val Ile Val Ser
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Glu Tyr Cys Leu Ser Ile His Tyr Gln His Gly Gly Val Ile Cys Thr
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cag gtc cac aag cag act atg gtc cag ctc gcc ctg cgg gtg gcg gat      860
Gln Val His Lys Gln Thr Met Val Gln Leu Ala Leu Arg Val Ala Asp
 117                               122                               127                               132

gaa atg gat gtt aac att ggt cat gag gtt ggc tac gtg atc cct ttc      908
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Val Ile Ile Leu Asp Asp Ile His Glu Arg Ser Ile Ala Thr Asp Val																
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Pro Leu Tyr Pro Lys Glu Lys Cys Ser Leu Phe Lys Pro Leu Asp Glu																
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Ser Ser Gly Glu Phe Leu Ile Trp Ser Asn Ser Val Arg Phe Val Ile																
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Asp Val Gly Val Glu Arg Arg Lys Val Tyr Asn Pro Arg Ile Arg Ala																
357					362					367					372	







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Ala Ile Thr Ser Glu Glu Arg Thr Lys His Asp Arg Gln Phe Asp Asn
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Gln	Cys	Asp	Leu	Glu	Ile	Met	Glu	Ile	Lys	Gln	Leu	Gln	Gln	Glu	Leu	
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 Val Phe Ile Pro Lys Glu Lys Pro Ile Glu Thr Arg Lys Glu Glu Lys  
 97 102 107 112

gtg acc ctt gac cca gaa ctg gaa gaa gct ttg gcc agt gcc tct gac 384  
 Val Thr Leu Asp Pro Glu Leu Glu Glu Ala Leu Ala Ser Ala Ser Asp  
 113 118 123 128



acttccttga ggagaagtga agtttcactg tggatggcc attgaaaaac aaaaactctt 1116  
 cttcttcccc atcaggacca ttttatcaaa gtctgttcat ttccgttaac cacataacta 1176  
 ataatttaat tggtattctt ttttagcact acttatttat cttggatttt gtaatatatg 1236  
 caattgtttt atttgctcat gggcacttct ggcaacttga caaatggacc gatgcagatt 1296  
 ttagagagtg acgacatgga aatgaattt aaccactttc ttaaaaaaaaaa aaaa 1350

<210> 114  
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 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (157)..(771)

<400> 114  
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 gagcgggaagg gccaaaggac gtcttctcca cgccgtccg actccagggg agccgtggcc 120  
 tcctctccgc cctagcgtg agaaccgtgg gtaccg atg gat gtg gcc gag agc 174  
 Met Asp Val Ala Glu Ser  
 1  
 cct gaa cgg gat cct cac tct cca gag gat gaa gag cag cca cag gga 222  
 Pro Glu Arg Asp Pro His Ser Pro Glu Asp Glu Glu Gln Pro Gln Gly  
 7 12 17 22  
 ctc tcg gac gat gac att ctg agg gac agc ggg tcc gat cag gat ttg 270  
 Leu Ser Asp Asp Asp Ile Leu Arg Asp Ser Gly Ser Asp Gln Asp Leu  
 23 28 33 38  
 gac ggg gcg ggg gtg agg gct tct gat ctg gag gat gag gaa agt gca 318  
 Asp Gly Ala Gly Val Arg Ala Ser Asp Leu Glu Asp Glu Glu Ser Ala  
 39 44 49 54  
 gcc agg ggg ccg agc cag gag gag gaa gat aat cac tcc gac gag gag 366  
 Ala Arg Gly Pro Ser Gln Glu Glu Glu Asp Asn His Ser Asp Glu Glu  
 55 60 65 70  
 gac cgg gca agt gag cct aaa tcc caa gac cag gac tca gag gtg aat 414  
 Asp Arg Ala Ser Glu Pro Lys Ser Gln Asp Gln Asp Ser Glu Val Asn  
 71 76 81 86  
 gag ctg agc cgg ggc ccg acc agc tcc ccc tgc gag gag gag ggg gac 462  
 Glu Leu Ser Arg Gly Pro Thr Ser Ser Pro Cys Glu Glu Glu Gly Asp  
 87 92 97 102  
 gaa ggg gag gaa gac cgg aca agc gac ctt agg gat gag gcc tcc tca 510  
 Glu Gly Glu Glu Asp Arg Thr Ser Asp Leu Arg Asp Glu Ala Ser Ser

103	108	113	118	
gtc acc agg gag ctg gat gag cat gag cta gac tac gat gag gag gtt				558
Val Thr Arg Glu Leu Asp Glu His Glu Leu Asp Tyr Asp Glu Glu Val				
119	124	129	134	
cct gag gag cca gct ccc gcc gtc cag gag gac gag gct gag aaa gcg				606
Pro Glu Glu Pro Ala Pro Ala Val Gln Glu Asp Glu Ala Glu Lys Ala				
135	140	145	150	
ggg gct gag gat gat gag gag aag ggc gaa ggc act ccc agg gag gag				654
Gly Ala Glu Asp Asp Glu Glu Lys Gly Glu Gly Thr Pro Arg Glu Glu				
151	156	161	166	
ggg aag gct ggt gtt cag agt gtg gga gaa aag gaa tcc ctg gag gct				702
Gly Lys Ala Gly Val Gln Ser Val Gly Glu Lys Glu Ser Leu Glu Ala				
167	172	177	182	
gcc aag gag aaa aag aaa gag gac gat gat gga gaa atc gaa ttt agt				750
Ala Lys Glu Lys Lys Lys Glu Asp Asp Asp Gly Glu Ile Glu Phe Ser				
183	188	193	198	
agt agt agg cgg ccg ctc tag ag gatccaagct tacgtacgcg tgcattgcgac				803
Ser Ser Arg Arg Pro Leu *				
199	204			
gtcatagctc ttctatagtg tcacctaaat gcgattcact taccgctaca tc				855

<210> 115  
 <211> 1973  
 <212> DNA  
 <213> Homo sapiens  
  
 <220>  
 <221> CDS  
 <222> (255)..(1784)

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atccactagt ccagtgtggt ggaattcgat ggaggacgca gaggcacgct gttgccatgg	120
cagtgtggtc ctggctgccg cggaggcagg tgccgggggtc tcctttgcct caatgtgaag	180
agcttaaaaa gaggaggaga ggagaactcc cccggccatc tctgtgatcc cagccgccgc	240
attttacaca gaaa atg aat gaa aat aaa gat act gat tca aag aaa agt	290
Met Asn Glu Asn Lys Asp Thr Asp Ser Lys Lys Ser	
1 5 10	
gaa gaa tac gaa gat gac ttt gaa aag gac ctg gag tgg tta att aat	338
Glu Glu Tyr Glu Asp Asp Phe Glu Lys Asp Leu Glu Trp Leu Ile Asn	
13 18 23 28	





Gln	Gln	Leu	Leu	Pro	Arg	Ser	Ser	Asn	Ser	Ser	Val	Ser	Gly	Thr	Lys	
253					258					263					268	
aaa	gaa	gat	tct	aca	gca	aag	att	cat	gct	gtc	act	cac	tca	tca	aca	1106
Lys	Glu	Asp	Ser	Thr	Ala	Lys	Ile	His	Ala	Val	Thr	His	Ser	Ser	Thr	
269					274					279					284	
gga	gag	ccg	ctg	gct	tat	atc	gct	cag	cca	cca	ctc	aac	cgc	aag	act	1154
Gly	Glu	Pro	Leu	Ala	Tyr	Ile	Ala	Gln	Pro	Pro	Leu	Asn	Arg	Lys	Thr	
285					290					295					300	
tgt	cca	agc	tct	gct	gtc	aac	tca	gat	cga	agt	aaa	ggg	aat	ggg	aaa	1202
Cys	Pro	Ser	Ser	Ala	Val	Asn	Ser	Asp	Arg	Ser	Lys	Gly	Asn	Gly	Lys	
301					306					311					316	
tct	aat	cac	agg	aca	cag	tct	gca	cat	atc	tca	cca	gtg	act	tca	aca	1250
Ser	Asn	His	Arg	Thr	Gln	Ser	Ala	His	Ile	Ser	Pro	Val	Thr	Ser	Thr	
317					322					327					332	
tac	tgt	ctt	tcc	cct	cga	cag	aaa	gaa	cta	caa	aaa	caa	cta	gaa	gaa	1298
Tyr	Cys	Leu	Ser	Pro	Arg	Gln	Lys	Glu	Leu	Gln	Lys	Gln	Leu	Glu	Glu	
333					338					343					348	
aag	aga	gaa	aaa	ctg	aaa	aga	gag	gaa	gag	cga	cga	aaa	ata	gaa	gaa	1346
Lys	Arg	Glu	Lys	Leu	Lys	Arg	Glu	Glu	Glu	Arg	Arg	Lys	Ile	Glu	Glu	
349					354					359					364	
gag	aaa	gaa	aaa	aag	aga	gag	aat	gac	ata	gta	ttt	aaa	gcg	tgg	ttg	1394
Glu	Lys	Glu	Lys	Lys	Arg	Glu	Asn	Asp	Ile	Val	Phe	Lys	Ala	Trp	Leu	
365					370					375					380	
caa	aag	aaa	aga	gag	cag	gtc	tta	gaa	atg	agg	aga	att	cag	cga	gca	1442
Gln	Lys	Lys	Arg	Glu	Gln	Val	Leu	Glu	Met	Arg	Arg	Ile	Gln	Arg	Ala	
381					386					391					396	
aag	gaa	att	gaa	gac	atg	aac	agt	aga	cag	gaa	aac	aga	gat	cca	caa	1490
Lys	Glu	Ile	Glu	Asp	Met	Asn	Ser	Arg	Gln	Glu	Asn	Arg	Asp	Pro	Gln	
397					402					407					412	
caa	gct	ttt	cga	tta	tgg	ctt	aaa	aaa	aag	cac	gaa	gag	cag	atg	aaa	1538
Gln	Ala	Phe	Arg	Leu	Trp	Leu	Lys	Lys	Lys	His	Glu	Glu	Gln	Met	Lys	
413					418					423					428	
gaa	aga	cag	aca	gaa	gaa	cta	aga	aag	caa	gag	gaa	tgt	tta	ttc	ttc	1586
Glu	Arg	Gln	Thr	Glu	Glu	Leu	Arg	Lys	Gln	Glu	Glu	Cys	Leu	Phe	Phe	
429					434					439					444	
ctt	aaa	gga	aca	gaa	ggc	cgg	gaa	agg	gcc	ttt	aaa	caa	tgg	tta	aga	1634
Leu	Lys	Gly	Thr	Glu	Gly	Arg	Glu	Arg	Ala	Phe	Lys	Gln	Trp	Leu	Arg	
445					450					455					460	
agg	aaa	cgg	atg	gaa	aaa	atg	gca	gag	caa	caa	gct	gtc	aga	gag	aga	1682
Arg	Lys	Arg	Met	Glu	Lys	Met	Ala	Glu	Gln	Gln	Ala	Val	Arg	Glu	Arg	
461					466					471					476	
act	aga	cag	ctc	cga	cta	gaa	gct	aag	cgt	tct	aaa	cag	tta	cag	cac	1730
Thr	Arg	Gln	Leu	Arg	Leu	Glu	Ala	Lys	Arg	Ser	Lys	Gln	Leu	Gln	His	

477	482	487	492	
cac cta tat atg tca gaa gcc aaa cct ttt cgt ttt act gat cat tat	1778			
His Leu Tyr Met Ser Glu Ala Lys Pro Phe Arg Phe Thr Asp His Tyr				
493	498	503	508	
aac tga aagtttctat taaatatttc agtgggcagc tgctatcaaa attttggata				1834
Asn *				
509				
tgatttctta gggctctgtgt actttgggtg tattctaaat tatggaaatg gtatttatct				1894
tttattgaca gtgaatttgt ttttttaata ctagaacaaa ataaattttt ttctcacagt				1954
gttgtaaaaa aaaaaaaaaa				1973

<210> 116  
 <211> 951  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (620)..(859)

<400> 116	
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cgacagtgcc cgatacagca ggcgctcaat aagtggcgaa tgaaagacag ggcaaggcgg	120
agagagaaga aacagaaagg gaaagagaaa gcccgggccg ccagagcgct taatcacacc	180
tggtcaggc tccacactgg tcctccagct cccttttctc agcgatggac tcacagcccc	240
acccggagcg ctggagcgcg gacgcggtca ctgcgctgc gcctcaccgc gctggcacc	300
cggcctggca gcctttgggg acctgaacca gctgcgcctg cgcaggtgga acgggtggaa	360
cgggtggggg agcggacagt cgaacggcct gagagggctc agctgggtccg gggctgcggc	420
gcctttgtga gcgcggccgc cggccaggat cgagccctgg cccgggccct ggcccagccc	480
cggcctccaa ggaccgcgcc gaaggaggtg cccactggag ggaggaggcg ctcgactttc	540
tcaggatact gtccctctcc cacagaggag ctgaaggagt aggacagaag aactgtcaaa	600
ttctggaatc cttaaagcc atg tcc aag gat ttg gtg aca ttt ggg gat gtg	652
Met Ser Lys Asp Leu Val Thr Phe Gly Asp Val	
1 5	
gct gta aat ttc tct caa gag gaa tgg gaa tgg ctg aac cct gct cag	700
Ala Val Asn Phe Ser Gln Glu Glu Trp Glu Trp Leu Asn Pro Ala Gln	
12 17 22 27	

agg aat ttg tac agg aaa gtg atg ttg gag aac tac agg agc ttg gta 748  
 Arg Asn Leu Tyr Arg Lys Val Met Leu Glu Asn Tyr Arg Ser Leu Val  
 28 33 38 43

tca ttg gga gtt tct gtt tct aag cca gat gtg atc tca tta ttg gag 796  
 Ser Leu Gly Val Ser Val Ser Lys Pro Asp Val Ile Ser Leu Leu Glu  
 44 49 54 59

caa gga aaa gag ccc tgg atg gtg aag aag gag gga aca aga ggc cca 844  
 Gln Gly Lys Glu Pro Trp Met Val Lys Lys Glu Gly Thr Arg Gly Pro  
 60 65 70 75

tgc cct ggt gag tga gagagaaata gggagacaga agccattgcc aggaagagct 899  
 Cys Pro Gly Glu \*  
 76

cagcaatttc tgaagatttc agttcataat tgacgtttcg tgggtagctc tt 951

<210> 117  
 <211> 508  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (116)..(328)

<400> 117

aaaatgtatg cggtactagc tggctagcgt tttaaacttaa gcttggtacc gagctcggat 60

ccactagtcc agtgtggtgg aattcgcggtt ttcggcgggc ttcccgggta caaaa atg 118  
 Met  
 1

gct gtg gct agc gat ttc tac ctg cgc tac tac gta ggg cac aag ggc 166  
 Ala Val Ala Ser Asp Phe Tyr Leu Arg Tyr Tyr Val Gly His Lys Gly  
 2 7 12 17

aag ttt ggg cac gag ttt ctg gag ttc gaa ttt cgg ccg gac ggt gag 214  
 Lys Phe Gly His Glu Phe Leu Glu Phe Glu Phe Arg Pro Asp Gly Glu  
 18 23 28 33

aag agg ccc acg gca cgc ggt gct ggg aaa ggg gag cga gac cga gag 262  
 Lys Arg Pro Thr Ala Arg Gly Ala Gly Lys Gly Glu Arg Asp Arg Glu  
 34 39 44 49

gcc ggg tgg tgt gga ggg tac agg cgg cgg agg cca ctg ctt ccc tcg 310  
 Ala Gly Trp Cys Gly Gly Tyr Arg Arg Arg Arg Pro Leu Leu Pro Ser  
 50 55 60 65

aag gaa ata gga gct taa gaatag aggaggcata agttgggtttt ataaatgaaa 364  
 Lys Glu Ile Gly Ala \*  
 66 71

gagaattaat tgcaataaat taaagctaat cctgtcacia actgaaaagt tgaacctaca 424  
gtaatcagaa ttctgtaaca gtgcaccaga agggactcta gatcgctgcc ctgattgaaa 484  
atgctagcac ttttttgaaa accg 508

<210> 118  
<211> 792  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (122)..(751)

<400> 118  
cactgagtcc ctcgtacggg cggaggaaga cctccgcgga cagacattgc aagacacccc 60  
tgctcctcgt tggcaagccg ccccatgatg aaggcctaca cctggtcacg gagacttttg 120  
g atg cag cct tta acg aag gac gca ggc atg agc ctg tcc tct gtg 166  
Met Gln Pro Leu Thr Lys Asp Ala Gly Met Ser Leu Ser Ser Val  
1 5 10  
acg ctg gcc agc gcc cta cag gtc agg ggt gaa gct ctg tct gag gag 214  
Thr Leu Ala Ser Ala Leu Gln Val Arg Gly Glu Ala Leu Ser Glu Glu  
16 21 26 31  
gaa atc tgg tcc ctc ctg ttc ctg gcc gct gag cag ctc ctg gaa gac 262  
Glu Ile Trp Ser Leu Leu Phe Leu Ala Ala Glu Gln Leu Leu Glu Asp  
32 37 42 47  
ctc cgc aac gat tcc tcg gac tat gtg gtt tgc ccc tgg tca gcc ctg 310  
Leu Arg Asn Asp Ser Ser Asp Tyr Val Val Cys Pro Trp Ser Ala Leu  
48 53 58 63  
ctt tct gca gct gga agc ctt tct ttc caa ggc cgt gtt tct cat ata 358  
Leu Ser Ala Ala Gly Ser Leu Ser Phe Gln Gly Arg Val Ser His Ile  
64 69 74 79  
gag gct gct cct ttc aag gcc cct gaa ctg cta cag gga cag agt gag 406  
Glu Ala Ala Pro Phe Lys Ala Pro Glu Leu Leu Gln Gly Gln Ser Glu  
80 85 90 95  
gat gag cag cct gat gca tct cag atg cat gtc tat tct tta gga atg 454  
Asp Glu Gln Pro Asp Ala Ser Gln Met His Val Tyr Ser Leu Gly Met  
96 101 106 111  
acc ctc tac tgg tca gca ggg ttt cat gtt ccg cca cat cag ccc ctg 502  
Thr Leu Tyr Trp Ser Ala Gly Phe His Val Pro Pro His Gln Pro Leu  
112 117 122 127  
cag ctc tgc gag ccc ctg cac tcc atc ctg ctg acc atg tgt gaa gac 550  
Gln Leu Cys Glu Pro Leu His Ser Ile Leu Leu Thr Met Cys Glu Asp

128		133		138		143	
cag cct cac agg cgg tgc acg ttg cag tcg gtt ctg gaa gct tgt cgg							598
Gln Pro His Arg Arg Cys Thr Leu Gln Ser Val Leu Glu Ala Cys Arg							
144		149		154		159	
gtt cat gag aaa gaa gtg tct gtc tac cca gcc cct gct ggt ctc cac							646
Val His Glu Lys Glu Val Ser Val Tyr Pro Ala Pro Ala Gly Leu His							
160		165		170		175	
atc aga agg ctg gtt ggc ttg gtt ctg ggt acc att tct gag gtc agt							694
Ile Arg Arg Leu Val Gly Leu Val Leu Gly Thr Ile Ser Glu Val Ser							
176		181		186		191	
aga gaa ccg tgc ttt tca agc agt agc tgc tgg tca tgt gtg gct att							742
Arg Glu Pro Cys Phe Ser Ser Ser Ser Cys Trp Ser Cys Val Ala Ile							
192		197		202		207	
aaa att tga attagttata ttatcattaa ctaaaataaaa ataaaaaaaa a							792
Lys Ile *							
208							

<210> 119  
 <211> 2136  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (309)..(1625)

<400> 119

aatgcaggac cgggtccggaa ttcccgggtc gacgatttcg tcgagggggg gttaaaggcc	60
cccaaaacat gcacacatga aaagggcaaa aagtaaccgt ccttgacagg gagtcttaac	120
tagagaagga aacggaacta aactggcggg ctccgtggaa gcgtggccgg cagcgtcccg	180
gacgaggaga gacagcgtct tgctcagtca cccaggctgg agtgcagtga tcatagctca	240
tcgcctcctt gaactcctgg gcttaagcta tcttcccgcc ttagcctcct gaatagctgg	300
gaccacag atg tct ttg gtg gac ttg gga aag agg ttg cta gaa gca gca	350
Met Ser Leu Val Asp Leu Gly Lys Arg Leu Leu Glu Ala Ala	
1 5 10	
aga aaa ggc caa gat gat gaa gtg aga acg ttg atg gca aat ggc gcc	398
Arg Lys Gly Gln Asp Asp Glu Val Arg Thr Leu Met Ala Asn Gly Ala	
15 20 25 30	
cca ttc acc aca gac tgg ttt tcc aaa ttg aga gtc tcc tgt gga tat	446
Pro Phe Thr Thr Asp Trp Phe Ser Lys Leu Arg Val Ser Cys Gly Tyr	
31 36 41 46	





agagaatttt cccttttttt tttttttttg gaaacaaagg ggattttaac ttcaaaaaaa 2130  
 aaaaaa 2136

<210> 120  
 <211> 1335  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(1335)

<400> 120

atg att gaa gac aat aag gag aac aaa gac cat tcc tta gaa agg gga 48  
 Met Ile Glu Asp Asn Lys Glu Asn Lys Asp His Ser Leu Glu Arg Gly  
 1 5 10

aga gca agt ctc att ttt tcc tta aag aat gaa gtt gga gga ctt ata 96  
 Arg Ala Ser Leu Ile Phe Ser Leu Lys Asn Glu Val Gly Gly Leu Ile  
 17 22 27 32

aaa gcc ctg aaa atc ttt cag gag aag cat gtg aat ctg tta cat atc 144  
 Lys Ala Leu Lys Ile Phe Gln Glu Lys His Val Asn Leu Leu His Ile  
 33 38 43 48

gag tcc cga aaa tca aaa aga aga aac tca gaa ttt gag att ttt gtt 192  
 Glu Ser Arg Lys Ser Lys Arg Arg Asn Ser Glu Phe Glu Ile Phe Val  
 49 54 59 64

gac tgt gac atc aac aga gaa caa ttg aat gat att ttt cat ctg ctg 240  
 Asp Cys Asp Ile Asn Arg Glu Gln Leu Asn Asp Ile Phe His Leu Leu  
 65 70 75 80

aag tct cat acc aat gtt ctc tct gtg aat cta cca gat aat ttt act 288  
 Lys Ser His Thr Asn Val Leu Ser Val Asn Leu Pro Asp Asn Phe Thr  
 81 86 91 96

ttg aag gaa gat ggt atg gaa act gtt cct tgg ttt cca aag aag att 336  
 Leu Lys Glu Asp Gly Met Glu Thr Val Pro Trp Phe Pro Lys Lys Ile  
 97 102 107 112

tct gac ctg gac cat tgt gcc aac aga gtt ctg atg tat gga tct gaa 384  
 Ser Asp Leu Asp His Cys Ala Asn Arg Val Leu Met Tyr Gly Ser Glu  
 113 118 123 128

cta gat gca gac cat cct ggc ttc aaa gac aat gtc tac cgt aaa cgt 432  
 Leu Asp Ala Asp His Pro Gly Phe Lys Asp Asn Val Tyr Arg Lys Arg  
 129 134 139 144

cga aag tat ttt gcg gac ttg gct atg aac tat aaa cat gga gac ccc 480  
 Arg Lys Tyr Phe Ala Asp Leu Ala Met Asn Tyr Lys His Gly Asp Pro  
 145 150 155 160





aag atg aga gaa ttt acc aaa aca att aag cgt ccc ttt gga gtg aaa	1200
Lys Met Arg Glu Phe Thr Lys Thr Ile Lys Arg Pro Phe Gly Val Lys	
385 390 395 400	
tat aat ccc tac aca cga agc att cag atc ctg aaa gac gcc aaa agc	1248
Tyr Asn Pro Tyr Thr Arg Ser Ile Gln Ile Leu Lys Asp Ala Lys Ser	
401 406 411 416	
ata acg aat gcc atg aac gag ctg cgg cat gat ctt gac gtt gtc agc	1296
Ile Thr Asn Ala Met Asn Glu Leu Arg His Asp Leu Asp Val Val Ser	
417 422 427 432	
gac gcc ctt ggg aag gtc agc agg aag ccg agt atc taa	1335
Asp Ala Leu Gly Lys Val Ser Arg Lys Pro Ser Ile *	
433 438 443	

<210> 121  
 <211> 3266  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (166)..(2742)

<400> 121

atcgattgca atagctatct attcgatgat gaagataccc caccaaacc aaaaaaagag	60
atctctcgag gatccgaatt cgcggtcgcg tccgcgtcgc cgccatcctc ggcgcgactc	120
gcttctttcg gttctacctg ggagaatcca ccgccatccg ccacc atg gtg aac	174
Met Val Asn	
1	
ttc acg gta gac cag atc cgc gcc atc atg gac aag aag gcc aac atc	222
Phe Thr Val Asp Gln Ile Arg Ala Ile Met Asp Lys Lys Ala Asn Ile	
4 9 14 19	
cgc aac atg tct gtc atc gcc cac gtg gac cat ggc aag tcc acg ctg	270
Arg Asn Met Ser Val Ile Ala His Val Asp His Gly Lys Ser Thr Leu	
20 25 30 35	
aca gac tcc ctg gtg tgc aag gcg ggc atc atc gcc tcg gcc cgg gcc	318
Thr Asp Ser Leu Val Cys Lys Ala Gly Ile Ile Ala Ser Ala Arg Ala	
36 41 46 51	
ggg gag aca cgc ttc act gat acc cgg aag gac gag cag gag cgt tgc	366
Gly Glu Thr Arg Phe Thr Asp Thr Arg Lys Asp Glu Gln Glu Arg Cys	
52 57 62 67	
atc acc atc aag tca act gcc atc tcc ctc ttc tac gag ctc tcg gag	414
Ile Thr Ile Lys Ser Thr Ala Ile Ser Leu Phe Tyr Glu Leu Ser Glu	
68 73 78 83	





Pro 532	Met	Val	Gln	Cys	Ile 537	Ile	Glu	Glu	Ser	Gly 542	Glu	His	Ile	Ile	Ala 547	
ggc 548	gcc	ggc	gag	ctg	cac 553	ctg	gag	atc	tgc	ctg 558	aag	gac	ctg	gag	gag 563	1854
Gly	Ala	Gly	Glu	Leu	His	Leu	Glu	Ile	Cys	Leu	Lys	Asp	Leu	Glu	Glu	
gac 564	cac	gcc	tgc	atc	ccc 569	atc	aag	aaa	tct	gac 574	ccg	gtc	gtc	tcg	tac 579	1902
Asp	His	Ala	Cys	Ile	Pro	Ile	Lys	Lys	Ser	Asp	Pro	Val	Val	Ser	Tyr	
cgc 580	gag	acg	gtc	agt	gaa 585	gag	tcg	aac	gtg	ctc 590	tgc	ctc	tcc	aag	tcc 595	1950
Arg	Glu	Thr	Val	Ser	Glu	Glu	Ser	Asn	Val	Leu	Cys	Leu	Ser	Lys	Ser	
ccc 596	aac	aag	cac	aac	cgg 601	ctg	tac	atg	aag	gcg 606	cgg	ccc	ttc	ccc	gac 611	1998
Pro	Asn	Lys	His	Asn	Arg	Leu	Tyr	Met	Lys	Ala	Arg	Pro	Phe	Pro	Asp	
ggc 612	ctg	gcc	gag	gac	atc 617	gat	aaa	ggc	gag	gtg 622	tcc	gcc	cgt	cag	gag 627	2046
Gly	Leu	Ala	Glu	Asp	Ile	Asp	Lys	Gly	Glu	Val	Ser	Ala	Arg	Gln	Glu	
ctc 628	aag	cag	cgg	gcg	cgc 633	tac	ctg	gcc	gag	aag 638	tac	gag	tgg	gac	gtg 643	2094
Leu	Lys	Gln	Arg	Ala	Arg	Tyr	Leu	Ala	Glu	Lys	Tyr	Glu	Trp	Asp	Val	
gct 644	gag	gcc	cgc	aag	atc 649	tgg	tgc	ttt	ggg	ccc 654	gac	ggc	acc	ggc	ccc 659	2142
Ala	Glu	Ala	Arg	Lys	Ile	Trp	Cys	Phe	Gly	Pro	Asp	Gly	Thr	Gly	Pro	
aac 660	atc	ctc	acc	gac	atc 665	acc	aag	ggc	gtg	cag 670	tac	ctc	aac	gag	atc 675	2190
Asn	Ile	Leu	Thr	Asp	Ile	Thr	Lys	Gly	Val	Gln	Tyr	Leu	Asn	Glu	Ile	
aag 676	gac	agt	gtg	gtg	gcc 681	ggc	ttc	cag	tgg	gcc 686	acc	aag	gag	ggc	gca 691	2238
Lys	Asp	Ser	Val	Val	Ala	Gly	Phe	Gln	Trp	Ala	Thr	Lys	Glu	Gly	Ala	
ctg 692	tgt	gag	gag	aac	atg 697	cgg	ggc	gtg	cgc	ttc 702	gac	gtc	cac	gac	gtc 707	2286
Leu	Cys	Glu	Glu	Asn	Met	Arg	Gly	Val	Arg	Phe	Asp	Val	His	Asp	Val	
acc 708	ctg	cac	gcc	gac	gcc 713	atc	cac	cgc	gga	ggg 718	ggc	cag	atc	atc	ccc 723	2334
Thr	Leu	His	Ala	Asp	Ala	Ile	His	Arg	Gly	Gly	Gly	Gln	Ile	Ile	Pro	
aca 724	gca	cgg	cgc	tgc	ctc 729	tac	gcc	agt	gtg	ctg 734	acc	gcc	cag	cca	cgc 739	2382
Thr	Ala	Arg	Arg	Cys	Leu	Tyr	Ala	Ser	Val	Leu	Thr	Ala	Gln	Pro	Arg	
ctc 740	atg	gag	ccc	atc	tac 745	ctt	gtg	gag	atc	cag 750	tgt	cca	gag	cag	gtg 755	2430
Leu	Met	Glu	Pro	Ile	Tyr	Leu	Val	Glu	Ile	Gln	Cys	Pro	Glu	Gln	Val	
gtc 740	ggc	ggc	atc	tac	ggg 745	gtt	ttg	aac	agg	aag 750	cgg	ggc	cac	gtg	ttc 755	2478
Val	Gly	Gly	Ile	Tyr	Gly	Val	Leu	Asn	Arg	Lys	Arg	Gly	His	Val	Phe	

756	761	766	771	
gag gag tcc cag gtg gcc ggc acc ccc atg ttt gtg gtc aag gcc tat				2526
Glu Glu Ser Gln Val Ala Gly Thr Pro Met Phe Val Val Lys Ala Tyr				
772	777	782	787	
ctg ccc gtc aac gag tcc ttt ggc ttc acc gct gac ctg agg tcc aac				2574
Leu Pro Val Asn Glu Ser Phe Gly Phe Thr Ala Asp Leu Arg Ser Asn				
788	793	798	803	
acg ggc ggc cag gcg ttc ccc cag tgt gtg ttt gac cac tgg cag atc				2622
Thr Gly Gly Gln Ala Phe Pro Gln Cys Val Phe Asp His Trp Gln Ile				
804	809	814	819	
ctg ccc gga gac ccc ttc gac aac agc agc cgc ccc agc cag gtg gtg				2670
Leu Pro Gly Asp Pro Phe Asp Asn Ser Ser Arg Pro Ser Gln Val Val				
820	825	830	835	
gcg gag acc cgc aag cgc aag ggc ctg aaa gaa ggc atc cct gcc ctg				2718
Ala Glu Thr Arg Lys Arg Lys Gly Leu Lys Glu Gly Ile Pro Ala Leu				
836	841	846	851	
gac aac ttc ctg gac aaa ttg tag gcggcccttc ctgcagcgcc tgccgccccg				2772
Asp Asn Phe Leu Asp Lys Leu *				
852	857			
gggactcgca gcacccacag caccacgtcc tcgaattctc agacgacacc tggagactgt				2832
cccgacacag cgacgctccc ctgagagggt tctggggccc gctgcgtgcc atcactcaac				2892
cataacactt gatgccgttt ctttcaatat ttatttccag agtccggagg cagcagacac				2952
gccctcttag tagggactta atgggccggt cggggagggg gaggcgggat gggacaccca				3012
acactttttc catttcttca gagggaaact cagatgtcca aactaatttt tcaaaaccta				3072
attttaacaa acgcattaag aggtttatatt gggtacatgg cccgcagtgg cttttgcccc				3132
agaaagggga aaggaacacg cgggtagatg atttctagca ggcaggaagt cctgtgcggt				3192
gtcaccatga gcacctccag ctgtactagt gccattggaa taataaattt gataagggtg				3252
tgaaaaaaaa aaaa				3266

<210> 122  
 <211> 833  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (174) .. (818)

<400> 122



Leu Asn Asn Glu Glu Gln Arg Glu Leu Gln Arg Leu Glu Lys Lys Lys  
 194 199 204 209

aaa aag atc ttt aat taa gcggccgcaa gctta 833  
 Lys Lys Ile Phe Asn \*  
 210 215

<210> 123  
 <211> 2385  
 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (103)..(1935)

<400> 123

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 ctggctttta aggaggacac ccggacacct ggaagctggg aa atg gac tca gtg 114  
 Met Asp Ser Val  
 1

gcc ttt gaa gat gtg gct gtg aac ttc aca caa gag gag tgg gct ttg 162  
 Ala Phe Glu Asp Val Ala Val Asn Phe Thr Gln Glu Glu Trp Ala Leu  
 5 10 15 20

ctg ggt cca tca cag aag agt ctc tac aga aat gtc atg cag gaa acc 210  
 Leu Gly Pro Ser Gln Lys Ser Leu Tyr Arg Asn Val Met Gln Glu Thr  
 21 26 31 36

att agg aac ctg gac tgt ata gaa atg aaa tgg gag gac cag aac att 258  
 Ile Arg Asn Leu Asp Cys Ile Glu Met Lys Trp Glu Asp Gln Asn Ile  
 37 42 47 52

gga gat cag tgc caa aat gcc aag aga aat cta aga agt cat aca tgt 306  
 Gly Asp Gln Cys Gln Asn Ala Lys Arg Asn Leu Arg Ser His Thr Cys  
 53 58 63 68

gaa att aaa gat gac agt caa tgt gga gaa act ttt ggc cag att cca 354  
 Glu Ile Lys Asp Asp Ser Gln Cys Gly Glu Thr Phe Gly Gln Ile Pro  
 69 74 79 84

gat agt att gtg aac aag aac act cct cga gta aat cca tgt gac agt 402  
 Asp Ser Ile Val Asn Lys Asn Thr Pro Arg Val Asn Pro Cys Asp Ser  
 85 90 95 100

ggt gag tgt gga gaa gtc gtc ttg ggt cat tcg tct ctt aat tgc aac 450  
 Gly Glu Cys Gly Glu Val Val Leu Gly His Ser Ser Leu Asn Cys Asn  
 101 106 111 116

atc aga gtt gac act gga cac aaa tca tgt gag cat cag gaa tat gga 498  
 Ile Arg Val Asp Thr Gly His Lys Ser Cys Glu His Gln Glu Tyr Gly







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aag ctg tat gaa tgt aag gaa tgt ggg aaa gca ttg agt tct ctc cgt      1890
Lys Leu Tyr Glu Cys Lys Glu Cys Gly Lys Ala Leu Ser Ser Leu Arg
581                      586                      591                      596

tcc ttg cat aga cat aaa agg act cac tgg aaa gat act ctc taa atg      1938
Ser Leu His Arg His Lys Arg Thr His Trp Lys Asp Thr Leu  *
597                      602                      607

tatggaatgt gggaaaacat tcagtacttt aatttcagaa acttgaaaga actcactttg      1998

gagatagacc ctatgaatgt aaacatggga taaagcctta agtagtttca attttttttaa      2058

atacagttat cccccaatat attgcagggg attgggtcca gcaccctcta aatccacaga      2118

tgccaagtcc tttgttatat ggcataatttg catgtaacct atgcatatcc tccagtatac      2178

tgtgtaaatac atctctagat gactttttaat acctcatgca ttgtaaaagc tatgtaaata      2238

gttgtttgat tgtattgttt agagaatcat gacaagaaaa atagtctcta catgttcgat      2298

gcagacacaa ccattgcagg cccacctacg tggatatatgt caccacagaac attaaaattt      2358

gttttaacat tcaaaaaaaaa aaaaaaa                                     2385

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<210> 124
<211> 1045
<212> DNA
<213> Homo sapiens

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<220>
<221> CDS
<222> (302)..(889)

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<400> 124

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gaaggcagct cgtggcgact gtccgtggtg ctgagcgccg gcgagagctg ggcgaggagcg      60

gctgatcggc tccctcgaac tggggagggtc cagtgggggtc gcttagggcc caaagccccc      120

accgggctcc aaaagctccc agggcctccc caggcacccg tgctcggccc ttccttcggt      180

cagaaagtcg cccctggggg gcagttcgtc ccaaagggtt tcctcgaaag aatctgagag      240

ggcgagctcc ttgaccgagg gaatctctct gtgtagcctt ggaagccgcc agccccagaa      300

g      atg cct gcc ttc aat aga ttg ttt ccc ctg gct tct ctc gtg ctt      346
      Met Pro Ala Phe Asn Arg Leu Phe Pro Leu Ala Ser Leu Val Leu
          1              5              10

atc tac tgg gtc agt gtc tgc ttc cct gtg tgt gtg gaa gtg ccc tcg      394
Ile Tyr Trp Val Ser Val Cys Phe Pro Val Cys Val Glu Val Pro Ser
    16              21              26              31

gag acg gag gcc gtg cag ggc aac ccc atg aag ctg cgc tgc atc tcc      442
Glu Thr Glu Ala Val Gln Gly Asn Pro Met Lys Leu Arg Cys Ile Ser

```





```

aaaaagtata tagaacagtt acttctaata atcagaaaga gatgttttat agaacatttc 810
tttaatatata agttagagat gtcttcatag gcagtatggc tatctttgcc acagaaacat 870
aagtaaaatt ttagagttct gttttccatg aggtcaaaaa tataatttat tcctcaaaaa 930
aaaaaa 936

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<210> 126
<211> 2124
<212> DNA
<213> Homo sapiens

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<220>
<221> CDS
<222> (235)..(1980)

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<400> 126
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gtagggcaag aaagggagag gggacaggag ggaaggggtgg gccaaagcgg tgagaaagga 120
gggccagcca gttgggtggg ggagagggcc gagggccggg ggcaggagtg cagggctctg 180
aggcgggggag aggagaggag agaagagccg cgggggggcc agcccggagc cagg atg 237
Met
1

ccc gcg ccg cgc gcc cgg gag cag ccc cgc gtg ccc ggg gag cgc cag 285
Pro Ala Pro Arg Ala Arg Glu Gln Pro Arg Val Pro Gly Glu Arg Gln
2 7 12 17

ccg ctg ctg cct cgc ggt gcg cgg ggc cct cga cgg tgg cgg cgg gcg 333
Pro Leu Leu Pro Arg Gly Ala Arg Gly Pro Arg Arg Trp Arg Arg Ala
18 23 28 33

gcg ggc gcg gcc gtg ctg ctg gtg gag atg ctg gag cgc gcc gcc ttc 381
Ala Gly Ala Ala Val Leu Leu Val Glu Met Leu Glu Arg Ala Ala Phe
34 39 44 49

ttc ggc gtc acc gcc aac ctc gtg ctg tac ctc aac agc acc aac ttc 429
Phe Gly Val Thr Ala Asn Leu Val Leu Tyr Leu Asn Ser Thr Asn Phe
50 55 60 65

aac tgg acc ggc gag cag gcg acg cgc gcc gcg ctg gta ttc ctg ggc 477
Asn Trp Thr Gly Glu Gln Ala Thr Arg Ala Ala Leu Val Phe Leu Gly
66 71 76 81

gcc tcc tac ctg ctg gcg ccc gtg ggc ggc tgg ctg gcc gac gtg tac 525
Ala Ser Tyr Leu Leu Ala Pro Val Gly Gly Trp Leu Ala Asp Val Tyr
82 87 92 97

ctg ggc cgc tac cgc gcg gtc gcg ctc agc ctg ctg ctc tac ctg gcc 573

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Leu	Gly	Arg	Tyr	Arg	Ala	Val	Ala	Leu	Ser	Leu	Leu	Leu	Tyr	Leu	Ala	
98					103					108					113	
gcc	tcg	ggc	ctg	ctg	ccc	gcc	acc	gcc	ttc	ccc	gac	ggc	cgc	agc	tcc	621
Ala	Ser	Gly	Leu	Leu	Pro	Ala	Thr	Ala	Phe	Pro	Asp	Gly	Arg	Ser	Ser	
114					119					124					129	
ttc	tgc	gga	gag	atg	ccc	gcg	tcg	ccg	ctg	gga	cct	gcc	tgc	ccc	tcg	669
Phe	Cys	Gly	Glu	Met	Pro	Ala	Ser	Pro	Leu	Gly	Pro	Ala	Cys	Pro	Ser	
130					135					140					145	
gcc	ggc	tgc	ccg	cgc	tcc	tcg	ccc	agc	ccc	tac	tgc	gcg	ccc	gtc	ctc	717
Ala	Gly	Cys	Pro	Arg	Ser	Ser	Pro	Ser	Pro	Tyr	Cys	Ala	Pro	Val	Leu	
146					151					156					161	
tac	gcg	ggc	ctg	ctg	cta	ctc	ggc	ctg	gcc	gcc	agc	tcc	gtc	cgg	agc	765
Tyr	Ala	Gly	Leu	Leu	Leu	Leu	Gly	Leu	Ala	Ala	Ser	Ser	Val	Arg	Ser	
162					167					172					177	
aac	ctc	acc	tcc	ttc	ggt	gcc	gac	cag	gtg	atg	gat	ctc	ggc	cgc	gac	813
Asn	Leu	Thr	Ser	Phe	Gly	Ala	Asp	Gln	Val	Met	Asp	Leu	Gly	Arg	Asp	
178					183					188					193	
gcc	acc	cgc	cgc	ttc	ttc	aac	tgg	ttt	tac	tgg	agc	atc	aac	ctg	ggt	861
Ala	Thr	Arg	Arg	Phe	Phe	Asn	Trp	Phe	Tyr	Trp	Ser	Ile	Asn	Leu	Gly	
194					199					204					209	
gct	gtg	ctg	tcg	ctg	ctg	gtg	gtg	gcg	ttt	att	cag	cag	aac	atc	agc	909
Ala	Val	Leu	Ser	Leu	Leu	Val	Val	Ala	Phe	Ile	Gln	Gln	Asn	Ile	Ser	
210					215					220					225	
ttc	ctg	ctg	ggc	tac	agc	atc	cct	gtg	ggc	tgt	gtg	ggc	ctg	gca	ttt	957
Phe	Leu	Leu	Gly	Tyr	Ser	Ile	Pro	Val	Gly	Cys	Val	Gly	Leu	Ala	Phe	
226					231					236					241	
ttc	atc	ttc	ctc	ttt	gcc	acc	ccc	gtc	ttc	atc	acc	aag	ccc	ccg	atg	1005
Phe	Ile	Phe	Leu	Phe	Ala	Thr	Pro	Val	Phe	Ile	Thr	Lys	Pro	Pro	Met	
242					247					252					257	
ggc	agc	caa	gtg	tcc	tct	atg	ctt	aag	ctc	gct	ctc	caa	aac	tgc	tgc	1053
Gly	Ser	Gln	Val	Ser	Ser	Met	Leu	Lys	Leu	Ala	Leu	Gln	Asn	Cys	Cys	
258					263					268					273	
ccc	cag	ctg	tgg	caa	cga	cac	tcg	gcc	aga	gac	cgt	caa	tgt	gcc	cgc	1101
Pro	Gln	Leu	Trp	Gln	Arg	His	Ser	Ala	Arg	Asp	Arg	Gln	Cys	Ala	Arg	
274					279					284					289	
gtg	ctg	gcc	gac	gag	agg	tct	ccc	cag	cca	ggg	gct	tcc	ccg	caa	gag	1149
Val	Leu	Ala	Asp	Glu	Arg	Ser	Pro	Gln	Pro	Gly	Ala	Ser	Pro	Gln	Glu	
290					295					300					305	
gac	atc	gcc	aac	ttc	cag	gtg	ctg	gtg	aag	atc	ttg	ccc	gtc	atg	gtg	1197
Asp	Ile	Ala	Asn	Phe	Gln	Val	Leu	Val	Lys	Ile	Leu	Pro	Val	Met	Val	
306					311					316					321	
acc	ctg	gtg	ccc	tac	tgg	atg	gtc	tac	ttc	cag	atg	cag	tcc	acc	tat	1245
Thr	Leu	Val	Pro	Tyr	Trp	Met	Val	Tyr	Phe	Gln	Met	Gln	Ser	Thr	Tyr	





cgc tat gag agg gcg tcc cag ggc cca gcc tcc cac agc cgt ttc agc 1965  
 Arg Tyr Glu Arg Ala Ser Gln Gly Pro Ala Ser His Ser Arg Phe Ser  
 562 567 572 577  
 agg gac agg ggc tga acaggcccta ttccagcccc cttgcttcac tctaccggac 2020  
 Arg Asp Arg Gly \*  
 578  
 agacggcagc agtcccagct ctggtttcct tctcggttta ttctgtaga atgaaatggt 2080  
 tcccataaat aaggggcatg agcccttcct caaaaaaaaa aaaa 2124

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 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (181) .. (2793)

<400> 127

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 tgccgggggcc gcgcgcgctg atctgcgagt gaagagggac gagggaaaag aaacaaagcc 120  
 acagacgcaa cttgagactc ccgcacccca aaagaagcac cagatcagca aaaaaagaag 180  
 atg ggc ccc ccg agc ctc gtg ctg tgc ttg ctg tcc gca act gtg ttc 228  
 Met Gly Pro Pro Ser Leu Val Leu Cys Leu Leu Ser Ala Thr Val Phe  
 1 5 10 15  
 tcc ctg ctg ggt gga agc tcg gcc ttc ctg tcg cac cac cgc ctg aaa 276  
 Ser Leu Leu Gly Gly Ser Ser Ala Phe Leu Ser His His Arg Leu Lys  
 17 22 27 32  
 ggc agg ttt cag agg gac cgc agg aac atc cgc ccc aac atc atc ctg 324  
 Gly Arg Phe Gln Arg Asp Arg Arg Asn Ile Arg Pro Asn Ile Ile Leu  
 33 38 43 48  
 gtg ctg acg gac gac cag gat gtg gag ctg ggt tcc atg cag gtg atg 372  
 Val Leu Thr Asp Asp Gln Asp Val Glu Leu Gly Ser Met Gln Val Met  
 49 54 59 64  
 aac aag acc cgg cgc atc atg gag cag ggc ggg gcg cac ttc atc aac 420  
 Asn Lys Thr Arg Arg Ile Met Glu Gln Gly Gly Ala His Phe Ile Asn  
 65 70 75 80  
 gcc ttc gtg acc aca ccc atg tgc tgc ccc tca cgc tcc tcc atc ctc 468  
 Ala Phe Val Thr Thr Pro Met Cys Cys Pro Ser Arg Ser Ser Ile Leu  
 81 86 91 96  
 acc ggc aag tac gtc cac aac cac aac acc tac acc aac aat gag aac 516

Thr 97	Gly	Lys	Tyr	Val	His 102	Asn	His	Asn	Thr	Tyr 107	Thr	Asn	Asn	Glu	Asn 112	
tgc Cys 113	tcc Ser	tcg Ser	ccc Pro	tcc Ser	tgg Trp 118	cag Gln	gca Ala	cag Gln	cac His	gag Glu 123	agc Ser	cgc Arg	acc Thr	ttt Phe	gcc Ala 128	564
gtg Val 129	tac Tyr	ctc Leu	aat Asn	agc Ser	act Thr 134	ggc Gly	tac Tyr	cgg Arg	aca Thr	gct Ala 139	ttc Phe	ttc Phe	ggg Gly	aag Lys	tat Tyr 144	612
ctt Leu 145	aat Asn	gaa Glu	tac Tyr	aac Asn	ggc Gly 150	tcc Ser	tac Tyr	gtg Val	cca Pro	ccc Pro 155	ggc Gly	tgg Trp	aag Lys	gag Glu	tgg Trp 160	660
gtc Val 161	gga Gly	ctc Leu	ctt Leu	aaa Lys	aac Asn 166	tcc Ser	cgc Arg	ttt Phe	tat Tyr	aac Asn 171	tac Tyr	acg Thr	ctg Leu	tgt Cys	cgg Arg 176	708
aac Asn 177	ggg Gly	gtg Val	aaa Lys	gag Glu	aag Lys 182	cac His	ggc Gly	tcc Ser	gac Asp	tac Tyr 187	tcc Ser	aag Lys	gat Asp	tac Tyr	ctc Leu 192	756
aca Thr 193	gac Asp	ctc Leu	atc Ile	acc Thr	aat Asn 198	gac Asp	agc Ser	gtg Val	agc Ser	ttc Phe 203	ttc Phe	cgc Arg	acg Thr	tcc Ser	aag Lys 208	804
aag Lys 209	atg Met	tac Tyr	ccg Pro	cac His	agg Arg 214	cca Pro	gtc Val	ctc Leu	atg Met	gtc Val 219	atc Ile	agc Ser	cat His	gca Ala	gcc Ala 224	852
ccc Pro 225	cac His	ggc Gly	cct Pro	gag Glu	gat Asp 230	tca Ser	gcc Ala	cca Pro	caa Gln	tat Tyr 235	tca Ser	cgc Arg	ctc Leu	ttc Phe	cca Pro 240	900
aac Asn 241	gca Ala	tct Ser	cag Gln	cac His	atc Ile 246	acg Thr	ccg Pro	agc Ser	tac Tyr	aac Asn 251	tac Tyr	gcg Ala	ccc Pro	aac Asn	ccg Pro 256	948
gac Asp 257	aaa Lys	cac His	tgg Trp	atc Ile	atg Met 262	cgc Arg	tac Tyr	acg Thr	ggg Gly	ccc Pro 267	atg Met	aag Lys	ccc Pro	atc Ile	cac His 272	996
atg Met 273	gaa Glu	ttc Phe	acc Thr	aac Asn	atg Met 278	ctc Leu	cag Gln	cgg Arg	aag Lys	cgc Arg 283	ttg Leu	cag Gln	acc Thr	ctc Leu	atg Met 288	1044
tcg Ser 289	gtg Val	gac Asp	gac Asp	tcc Ser	atg Met 294	gag Glu	acg Thr	att Ile	tac Tyr	aac Asn 299	atg Met	ctg Leu	gtt Val	gag Glu	acg Thr 304	1092
ggc Gly 305	gag Glu	ctg Leu	gac Asp	aac Asn	acg Thr 310	tac Tyr	atc Ile	gta Val	tac Tyr	acc Thr 315	gcc Ala	gac Asp	cac His	ggg Gly	tac Tyr 320	1140
cac His	atc Ile	ggc Gly	cag Gln	ttt Phe	ggc Gly	ctg Leu	gtg Val	aaa Lys	ggg Gly	aaa Lys	tcc Ser	atg Met	cca Pro	tat Tyr	gag Glu	1188

321						326						331						336					
ttt	gac	atc	agg	gtc	ccg	ttc	tac	gtg	agg	ggc	ccc	aac	gtg	gaa	gcc		1236						
Phe	Asp	Ile	Arg	Val	Pro	Phe	Tyr	Val	Arg	Gly	Pro	Asn	Val	Glu	Ala								
337						342						347						352					
ggc	tgt	ctg	aat	ccc	cac	atc	gtc	ctc	aac	att	gac	ctg	gcc	ccc	acc		1284						
Gly	Cys	Leu	Asn	Pro	His	Ile	Val	Leu	Asn	Ile	Asp	Leu	Ala	Pro	Thr								
353						358						363						368					
atc	ctg	gac	att	gca	ggc	ctg	gac	ata	cct	gcg	gat	atg	gac	ggg	aaa		1332						
Ile	Leu	Asp	Ile	Ala	Gly	Leu	Asp	Ile	Pro	Ala	Asp	Met	Asp	Gly	Lys								
369						374						379						384					
tcc	atc	ctc	aag	ctg	ctg	gac	acg	gag	cgg	ccg	gtg	aat	cgg	ttt	cac		1380						
Ser	Ile	Leu	Lys	Leu	Leu	Asp	Thr	Glu	Arg	Pro	Val	Asn	Arg	Phe	His								
385						390						395						400					
ttg	aaa	aag	aag	atg	agg	gtc	tgg	cgg	gac	tcc	ttc	ttg	gtg	gag	aga		1428						
Leu	Lys	Lys	Lys	Met	Arg	Val	Trp	Arg	Asp	Ser	Phe	Leu	Val	Glu	Arg								
401						406						411						416					
ggc	aag	ctg	cta	cac	aag	aga	gac	aat	gac	aag	gtg	gac	gcc	cag	gag		1476						
Gly	Lys	Leu	Leu	His	Lys	Arg	Asp	Asn	Asp	Lys	Val	Asp	Ala	Gln	Glu								
417						422						427						432					
gag	aac	ttt	ctg	ccc	aag	tac	cag	cgt	gtg	aag	gac	ctg	tgt	cag	cgt		1524						
Glu	Asn	Phe	Leu	Pro	Lys	Tyr	Gln	Arg	Val	Lys	Asp	Leu	Cys	Gln	Arg								
433						438						443						448					
gct	gag	tac	cag	acg	gcg	tgt	gag	cag	ctg	gga	cag	aag	tgg	cag	tgt		1572						
Ala	Glu	Tyr	Gln	Thr	Ala	Cys	Glu	Gln	Leu	Gly	Gln	Lys	Trp	Gln	Cys								
449						454						459						464					
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Val	Glu	Asp	Ala	Thr	Gly	Lys	Leu	Lys	Leu	His	Lys	Cys	Lys	Gly	Pro								
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atg	cgg	ctg	ggc	ggc	agc	aga	gcc	ctc	tcc	aac	ctc	gtg	ccc	aag	tac		1668						
Met	Arg	Leu	Gly	Gly	Ser	Arg	Ala	Leu	Ser	Asn	Leu	Val	Pro	Lys	Tyr								
481						486						491						496					
tac	ggg	cag	ggc	agc	gag	gcc	tgc	acc	tgt	gac	agc	ggg	gac	tac	aag		1716						
Tyr	Gly	Gln	Gly	Ser	Glu	Ala	Cys	Thr	Cys	Asp	Ser	Gly	Asp	Tyr	Lys								
497						502						507						512					
ctc	agc	ctg	gcc	gga	cgc	cgg	aaa	aaa	ctc	ttc	aag	aag	aag	tac	aag		1764						
Leu	Ser	Leu	Ala	Gly	Arg	Arg	Lys	Lys	Leu	Phe	Lys	Lys	Lys	Tyr	Lys								
513						518						523						528					
gcc	agc	tat	gtc	cgc	agt	cgc	tcc	atc	cgc	tca	gtg	gcc	atc	gag	gtg		1812						
Ala	Ser	Tyr	Val	Arg	Ser	Arg	Ser	Ile	Arg	Ser	Val	Ala	Ile	Glu	Val								
529						534						539											

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gcc Ala 593	gcc Ala	aac Asn	ccc Pro	att Ile	aaa Lys 598	gtg Val	aca Thr	cat His	cgg Arg	tgc Cys 603	tac Tyr	atc Ile	cta Leu	gag Glu	aac Asn 608	2004
gac Asp 609	aca Thr	gtc Val	cag Gln	tgt Cys	gac Asp 614	ctg Leu	gac Asp	ctg Leu	tac Tyr	aag Lys 619	tcc Ser	ctg Leu	cag Gln	gcc Ala	tgg Trp 624	2052
aaa Lys 625	gac Asp	cac His	aag Lys	ctg Leu	cac His 630	atc Ile	gac Asp	cac His	gag Glu	att Ile 635	gaa Glu	acc Thr	ctg Leu	cag Gln	aac Asn 640	2100
aaa Lys 641	att Ile	aag Lys	aac Asn	ctg Leu	agg Arg 646	gaa Glu	gtc Val	cga Arg	ggg Gly	cac His 651	ctg Leu	aag Lys	aaa Lys	aag Lys	cgg Arg 656	2148
cca Pro 657	gaa Glu	gaa Glu	tgt Cys	gac Asp	tgt Cys 662	cac His	aaa Lys	atc Ile	agc Ser	tac Tyr 667	cac His	acc Thr	cag Gln	cac His	aaa Lys 672	2196
ggc Gly 673	cgc Arg	ctc Leu	aag Lys	cac His	aga Arg 678	ggc Gly	tcc Ser	agt Ser	ctg Leu	cat His 683	cct Pro	ttc Phe	agg Arg	aag Lys	ggc Gly 688	2244
ctg Leu 689	caa Gln	gag Glu	aag Lys	gac Asp	aag Lys 694	gtg Val	tgg Trp	ctg Leu	ttg Leu	cgg Arg 699	gag Glu	cag Gln	aag Lys	cgc Arg	aag Lys 704	2292
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agc Ser 721	atg Met	cca Pro	ggc Gly	ctc Leu	acg Thr 726	tgc Cys	ttc Phe	acc Thr	cac His	gac Asp 731	aac Asn	cag Gln	cac His	tgg Trp	cag Gln 736	2388
acg Thr 737	gcg Ala	cct Pro	ttc Phe	tgg Trp	aca Thr 742	ctg Leu	ggg Gly	cct Pro	ttc Phe	tgt Cys 747	gcc Ala	tgc Cys	acc Thr	agc Ser	gcc Ala 752	2436
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ttc Phe 769	ctc Leu	ttc Phe	tgt Cys	gaa Glu	ttt Phe 774	gca Ala	act Thr	ggc Gly	ttc Phe	cta Leu 779	gag Glu	tac Tyr	ttt Phe	gat Asp	ctc Leu 784	2532

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Asn Thr Asp Pro Tyr Gln Leu Met Asn Ala Val Asn Thr Leu Asp Arg	
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gat gtc ctc aac cag cta cac gta cag ctc atg gag ctg agg agc tgc	2628
Asp Val Leu Asn Gln Leu His Val Gln Leu Met Glu Leu Arg Ser Cys	
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aag ggt tac aag cag tgt aac ccc cgg act cga aac atg gac ctg gga	2676
Lys Gly Tyr Lys Gln Cys Asn Pro Arg Thr Arg Asn Met Asp Leu Gly	
817 822 827 832	
ctt aaa gat gga gga agc tat gag caa tac agg cag ttt cag cgt cga	2724
Leu Lys Asp Gly Gly Ser Tyr Glu Gln Tyr Arg Gln Phe Gln Arg Arg	
833 838 843 848	
aag tgg cca gaa atg aag aga cct tct tcc aaa tca ctg gga caa ctg	2772
Lys Trp Pro Glu Met Lys Arg Pro Ser Ser Lys Ser Leu Gly Gln Leu	
849 854 859 864	
tgg gaa ggc tgg gaa ggt taa ga aacaacagag gtggacctcc aaaaacatag	2825
Trp Glu Gly Trp Glu Gly *	
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acagacgcaa cttgagactc ccgcatccca aaagaagcac cagatcagca aaaaaagaag      180

atg ggc ccc ccg agc ctc gtg ctg tgc ttg ctg tcc gca act gtg ttc      228
Met Gly Pro Pro Ser Leu Val Leu Cys Leu Leu Ser Ala Thr Val Phe
   1                               5                               10                               15

tcc ctg ctg ggt gga agc tcg gcc ttc ctg tcg cac cac cgc ctg aaa      276
Ser Leu Leu Gly Gly Ser Ser Ala Phe Leu Ser His His Arg Leu Lys
  17                               22                               27                               32

ggc agg ttt cag agg gac cgc agg aac atc cgc ccc aac atc atc ctg      324
Gly Arg Phe Gln Arg Asp Arg Arg Asn Ile Arg Pro Asn Ile Ile Leu
  33                               38                               43                               48

gtg ctg acg gac gac cag gat gtg gag ctg ggt tcc atg cag gtg atg      372
Val Leu Thr Asp Asp Gln Asp Val Glu Leu Gly Ser Met Gln Val Met
  49                               54                               59                               64

aac aag acc cgg cgc atc atg gag cag ggc ggg gcg cac ttc atc aac      420
Asn Lys Thr Arg Arg Ile Met Glu Gln Gly Gly Ala His Phe Ile Asn
  65                               70                               75                               80

gcc ttc gtg acc aca ccc atg tgc tgc ccc tca cgc tcc tcc atc ctc      468
Ala Phe Val Thr Thr Pro Met Cys Cys Pro Ser Arg Ser Ser Ile Leu
  81                               86                               91                               96

acc ggc aag tac gtc cac aac cac aac acc tac acc aac aat gag aac      516
Thr Gly Lys Tyr Val His Asn His Asn Thr Tyr Thr Asn Asn Glu Asn
  97                               102                               107                               112

tgc tcc tcg ccc tcc tgg cag gca cag cac gag agc cgc acc ttt gcc      564
Cys Ser Ser Pro Ser Trp Gln Ala Gln His Glu Ser Arg Thr Phe Ala
 113                               118                               123                               128

gtg tac ctc aat agc act ggc tac cgg aca gct ttc ttc ggg aag tat      612
Val Tyr Leu Asn Ser Thr Gly Tyr Arg Thr Ala Phe Phe Gly Lys Tyr
 129                               134                               139                               144

ctt aat gaa tac aac ggc tcc tac gtg cca ccc ggc tgg aag gag tgg      660
Leu Asn Glu Tyr Asn Gly Ser Tyr Val Pro Pro Gly Trp Lys Glu Trp
 145                               150                               155                               160

gtc gga ctc ctt aaa aac tcc cgc ttt tat aac tac acg ctg tgt cgg      708
Val Gly Leu Leu Lys Asn Ser Arg Phe Tyr Asn Tyr Thr Leu Cys Arg
 161                               166                               171                               176

aac ggg gtg aaa gag aag cac ggc tcc gac tac tcc aag gat tac ctc      756
Asn Gly Val Lys Glu Lys His Gly Ser Asp Tyr Ser Lys Asp Tyr Leu
 177                               182                               187                               192

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aca Thr 193	gac Asp	ctc Leu	atc Ile	acc Thr	aat Asn 198	gac Asp	agc Ser	gtg Val	agc Ser	ttc Phe 203	ttc Phe	cgc Arg	acg Thr	tcc Ser	aag Lys 208	804
aag Lys 209	atg Met	tac Tyr	ccg Pro	cac His	agg Arg 214	cca Pro	gtc Val	ctc Leu	atg Met	gtc Val 219	atc Ile	agc Ser	cat His	gca Ala	gcc Ala 224	852
ccc Pro 225	cac His	ggc Gly	cct Pro	gag Glu	gat Asp 230	tca Ser	gcc Ala	cca Pro	caa Gln	tat Tyr 235	tca Ser	cgc Arg	ctc Leu	ttc Phe	cca Pro 240	900
aac Asn 241	gca Ala	tct Ser	cag Gln	cac His	atc Ile 246	acg Thr	ccg Pro	agc Ser	tac Tyr	aac Asn 251	tac Tyr	gcg Ala	ccc Pro	aac Asn	ccg Pro 256	948
gac Asp 257	aaa Lys	cac His	tgg Trp	atc Ile	atg Met 262	cgc Arg	tac Tyr	acg Thr	ggg Gly	ccc Pro 267	atg Met	aag Lys	ccc Pro	atc Ile	cac His 272	996
atg Met 273	gaa Glu	ttc Phe	acc Thr	aac Asn	atg Met 278	ctc Leu	cag Gln	cgg Arg	aag Lys	cgc Arg 283	ttg Leu	cag Gln	acc Thr	ctc Leu	atg Met 288	1044
tcg Ser 289	gtg Val	gac Asp	gac Asp	tcc Ser	atg Met 294	gag Glu	acg Thr	att Ile	tac Tyr	aac Asn 299	atg Met	ctg Leu	gtt Val	gag Glu	acg Thr 304	1092
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cac His 321	atc Ile	ggc Gly	cag Gln	ttt Phe	ggc Gly 326	ctg Leu	gtg Val	aaa Lys	ggg Gly	aaa Lys 331	tcc Ser	atg Met	cca Pro	tat Tyr	gag Glu 336	1188
ttt Phe 337	gac Asp	atc Ile	agg Arg	gtc Val	ccg Pro 342	ttc Phe	tac Tyr	gtg Val	agg Arg	ggc Gly 347	ccc Pro	aac Asn	gtg Val	gaa Glu	gcc Ala 352	1236
ggc Gly 353	tgt Cys	ctg Leu	aat Asn	ccc Pro	cac His 358	atc Ile	gtc Val	ctc Leu	aac Asn	att Ile 363	gac Asp	ctg Leu	gcc Ala	ccc Pro	acc Thr 368	1284
atc Ile 369	ctg Leu	gac Asp	att Ile	gca Ala	ggc Gly 374	ctg Leu	gac Asp	ata Ile	cct Pro	gcg Ala 379	gat Asp	atg Met	gac Asp	ggg Gly	aaa Lys 384	1332
tcc Ser 385	atc Ile	ctc Leu	aag Lys	ctg Leu	ctg Leu 390	gac Asp	acg Thr	gag Glu	cgg Arg	ccg Pro 395	gtg Val	aat Asn	cgg Arg	ttt Phe	cac His 400	1380
ttg Leu 401	aaa Lys	aag Lys	aag Lys	atg Met	agg Arg 406	gtc Val	tgg Trp	cgg Arg	gac Asp	tcc Ser 411	ttc Phe	ttg Leu	gtg Val	gag Glu	aga Arg 416	1428





Lys 641	Ile	Lys	Asn	Leu	Arg 646	Glu	Val	Arg	Gly	His 651	Leu	Lys	Lys	Lys	Arg 656		
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Pro	Glu	Glu	Cys	Asp	Cys	His	Lys	Ile	Arg	Lys	Gly	Leu	Gln	Glu	Lys		
					662					667					672		
gac 673	aag	gtg	tgg	ctg	ttg	cgg	gag	cag	aag	cgc	aag	aag	aaa	ctc	cgc	2244	
Asp	Lys	Val	Trp	Leu	Leu	Arg	Glu	Gln	Lys	Arg	Lys	Lys	Lys	Leu	Arg		
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Lys	Leu	Leu	Lys	Arg	Leu	Gln	Asn	Asn	Asp	Thr	Cys	Ser	Met	Pro	Gly		
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ctc 705	acg	tgc	ttc	acc	cac	gac	aac	cag	cac	tgg	cag	acg	gcg	cct	ttc	2340	
Leu	Thr	Cys	Phe	Thr	His	Asp	Asn	Gln	His	Trp	Gln	Thr	Ala	Pro	Phe		
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tgg 721	aca	ctg	ggg	cct	ttc	tgt	gcc	tgc	acc	agc	gcc	aac	aat	aac	acg	2388	
Trp	Thr	Leu	Gly	Pro	Phe	Cys	Ala	Cys	Thr	Ser	Ala	Asn	Asn	Asn	Thr		
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tac 737	tgg	tgc	atg	agg	acc	atc	aat	gag	act	cac	aat	ttc	ctc	ttc	tgt	2436	
Tyr	Trp	Cys	Met	Arg	Thr	Ile	Asn	Glu	Thr	His	Asn	Phe	Leu	Phe	Cys		
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gaa 753	ttt	gca	act	ggc	ttc	cta	gag	tac	ttt	gat	ctc	aac	aca	gac	ccc	2484	
Glu	Phe	Ala	Thr	Gly	Phe	Leu	Glu	Tyr	Phe	Asp	Leu	Asn	Thr	Asp	Pro		
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tac 769	cag	ctg	atg	aat	gca	gtg	aac	aca	ctg	gac	agg	gat	gtc	ctc	aac	2532	
Tyr	Gln	Leu	Met	Asn	Ala	Val	Asn	Thr	Leu	Asp	Arg	Asp	Val	Leu	Asn		
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cag 785	cta	cac	gta	cag	ctc	atg	gag	ctg	agg	agc	tgc	aag	ggc	tac	aag	2580	
Gln	Leu	His	Val	Gln	Leu	Met	Glu	Leu	Arg	Ser	Cys	Lys	Gly	Tyr	Lys		
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Gln	Cys	Asn	Pro	Arg	Thr	Arg	Asn	Met	Asp	Leu	Gly	Leu	Lys	Asp	Gly		
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gga 817	agc	tat	gag	caa	tac	agg	cag	ttt	cag	cgt	cga	aag	tgg	cca	gaa	2676	
Gly	Ser	Tyr	Glu	Gln	Tyr	Arg	Gln	Phe	Gln	Arg	Arg	Lys	Trp	Pro	Glu		
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atg 833	aag	aga	cct	tct	tcc	aaa	tca	ctg	gga	caa	ctg	tgg	gaa	ggc	tgg	2724	
Met	Lys	Arg	Pro	Ser	Ser	Lys	Ser	Leu	Gly	Gln	Leu	Trp	Glu	Gly	Trp		
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Glu	Gly	*															
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Thr Thr Phe Val Val Tyr Glu Asn Thr Tyr Met Asn Ile Thr Leu Pro
17 22 27 32

cca cca ttc cag cat cct gac ctc agt cca ttg ctt aga tat agt ttt 144
Pro Pro Phe Gln His Pro Asp Leu Ser Pro Leu Leu Arg Tyr Ser Phe
33 38 43 48

gaa acc atg gct ccc act ggt ttg agt tcc ttg acc gtg aat agt aca 192
Glu Thr Met Ala Pro Thr Gly Leu Ser Ser Leu Thr Val Asn Ser Thr
49 54 59 64

gct gtg ccc aca aca cca gca gca ttt aag agc cta aac ttg cct ctt 240
Ala Val Pro Thr Thr Pro Ala Ala Phe Lys Ser Leu Asn Leu Pro Leu
65 70 75 80

cag atc acc ctt tct gct ata atg ata ttc att ctg ttt gtg tct ttt 288
Gln Ile Thr Leu Ser Ala Ile Met Ile Phe Ile Leu Phe Val Ser Phe
81 86 91 96

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Ala Val Phe Ile Val Cys Trp Ala Pro Phe Thr Thr Tyr Ser Leu Val	
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Ala Thr Phe Ser Lys His Phe Tyr Tyr Gln His Asn Phe Phe Glu Ile	
337 342 347 352	
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Ser Thr Trp Leu Leu Trp Leu Cys Tyr Leu Lys Ser Ala Leu Asn Pro	
353 358 363 368	
ctg atc tac tac tgg agg att aag aaa ttc cat gat gct tgc ctg gac	1152
Leu Ile Tyr Tyr Trp Arg Ile Lys Lys Phe His Asp Ala Cys Leu Asp	
369 374 379 384	
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Ser Leu Val Leu Ala Phe Leu Gly Val Cys Leu Gly Ile Thr Leu Ala	
17 22 27 32	
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Val Asp Arg Ser Asn Phe Lys Thr Cys Glu Glu Ser Ser Phe Cys Lys	
33 38 43 48	
cga cag aga agc ata cgg cca ggc ctc tct cca tac cga gcc ttg ctg	192
Arg Gln Arg Ser Ile Arg Pro Gly Leu Ser Pro Tyr Arg Ala Leu Leu	
49 54 59 64	



Leu	Tyr	Asn	Pro	Met	Ala	Leu	Tyr	Gly	Ser	Val	Pro	Val	Leu	Leu	Ala	
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His	Asn	Pro	His	Arg	Asp	Leu	Gly	Ile	Phe	Trp	Leu	Asn	Ala	Ala	Glu	
305					310					315					320	
acc	tgg	gtt	gat	ata	tct	tcc	aac	act	gcc	ggg	aag	acc	ctg	ttt	ggg	1008
Thr	Trp	Val	Asp	Ile	Ser	Ser	Asn	Thr	Ala	Gly	Lys	Thr	Leu	Phe	Gly	
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Lys	Met	Met	Asp	Tyr	Leu	Gln	Gly	Ser	Gly	Glu	Thr	Pro	Gln	Thr	Asp	
337					342					347					352	
gtt	cgc	tgg	atg	tca	gag	act	ggc	atc	att	gac	gtc	ttc	ctg	ctg	ctg	1104
Val	Arg	Trp	Met	Ser	Glu	Thr	Gly	Ile	Ile	Asp	Val	Phe	Leu	Leu	Leu	
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369					374					379					384	
acc	cag	gcg	ttg	ccc	cca	ctc	ttc	tcc	ctc	ggc	tac	cac	cag	agc	cgt	1200
Thr	Gln	Ala	Leu	Pro	Pro	Leu	Phe	Ser	Leu	Gly	Tyr	His	Gln	Ser	Arg	
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Val Asn Thr Ala Asn Glu Ala Arg Glu Val Ala Phe Asp Leu Glu Ile  
76 81 86 91

gca ttt atc gga gac ata aag gac aag gtg act gca tgg aag cag tac 446  
Ala Phe Ile Gly Asp Ile Lys Asp Lys Val Thr Ala Trp Lys Gln Tyr  
108 113 118 123

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Gly Arg Thr Met Glu Gln Phe Ile Ile His Leu Thr Val Asn Pro Gln  
140 145 150 155

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His	Met	Gln	Tyr	Glu	Ile	Val	Ile	Lys	Val	Lys	Pro	Lys	Gln	Leu	Val	
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466

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Thr Ile Lys Lys Ser Phe Ser Gly Lys Lys Gly His Val Leu Phe Arg				
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ccc acc gtg agc cag cag cag tcc tgc ccc aca tgc tct aca tcc tta				830
Pro Thr Val Ser Gln Gln Gln Ser Cys Pro Thr Cys Ser Thr Ser Leu				
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ctg aac ggg cac ttc aag gtg acc tac gat gtc agt cga gac aag atc				878
Leu Asn Gly His Phe Lys Val Thr Tyr Asp Val Ser Arg Asp Lys Ile				
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Cys Asp Leu Leu Val Ala Asn Asn His Phe Ala His Phe Phe Ala Pro				
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caa aac ctg aca aac atg aac aag aac gtg gtt ttt gtg att gac atc				974
Gln Asn Leu Thr Asn Met Asn Lys Asn Val Val Phe Val Ile Asp Ile				
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Ser Gly Ser Met Arg Gly Gln Lys Val Lys Gln Thr Lys Glu Ala Leu				
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Leu Lys Ile Leu Gly Asp Ile His Pro Gly Asp Tyr Phe Asp Leu Val				
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Leu Phe Gly Thr Arg Val Gln Ser Trp Lys Gly Ser Leu Val Gln Ala				
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Ser Glu Ala Asn Leu Gln Ala Ala Gln Asp Phe Val Arg Gly Phe Ser				
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Leu Asp Glu Ala Thr Asn Leu Asn Gly Gly Leu Leu Arg Gly Ile Glu				
364	369	374	379	
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Ile Leu Asn Gln Val Gln Glu Ser Leu Pro Glu Leu Ser Asn His Ala				
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Ser Ile Leu Ile Met Leu Thr Asp Gly Asp Pro Thr Glu Gly Val Thr				
396	401	406	411	
gac cgt tcc caa atc ctc aag aac gtc cgc aac gcc atc cgg ggc agg				1358
Asp Arg Ser Gln Ile Leu Lys Asn Val Arg Asn Ala Ile Arg Gly Arg				
412	417	422	427	





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agtcgcagg g atg aac ctc gag ttg ctg gag tcc ttt ggg cag aac tat 170  
Met Asn Leu Glu Leu Leu Glu Ser Phe Gly Gln Asn Tyr  
1 5 10  
cca gag gaa gct gat gga act ttg gat tgt atc agc atg gct ttg act 218  
Pro Glu Glu Ala Asp Gly Thr Leu Asp Cys Ile Ser Met Ala Leu Thr  
14 19 24 29  
tgc acc ttt aac agg tgg ggc aca ctg ctt gca gtt ggc tgt aat gat 266  
Cys Thr Phe Asn Arg Trp Gly Thr Leu Leu Ala Val Gly Cys Asn Asp  
30 35 40 45  
ggc cga att gtc atc tgg gat ttc ttg aca aga ggc att gct aaa att 314  
Gly Arg Ile Val Ile Trp Asp Phe Leu Thr Arg Gly Ile Ala Lys Ile  
46 51 56 61  
aaa ttt agt gca cac atc cat cca gtg tgt tct tta tgc tgg agc cga 362  
Lys Phe Ser Ala His Ile His Pro Val Cys Ser Leu Cys Trp Ser Arg  
62 67 72 77  
gat ggt cat aaa ctc gtg agt gct tcc act gat aac ata gtg tca cag 410  
Asp Gly His Lys Leu Val Ser Ala Ser Thr Asp Asn Ile Val Ser Gln  
78 83 88 93  
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Trp Asp Val Leu Ser Gly Asp Cys Asp Gln Arg Phe Arg Phe Pro Ser  
94 99 104 109  
ccc atc tta aaa gtc caa tat cat cca cga gat cag aac aag gtt ctc 506  
Pro Ile Leu Lys Val Gln Tyr His Pro Arg Asp Gln Asn Lys Val Leu  
110 115 120 125  
gtg tgt ccc atg aaa tct gct cct gtc atg ttg acc ctt tca gat tcc 554  
Val Cys Pro Met Lys Ser Ala Pro Val Met Leu Thr Leu Ser Asp Ser  
126 131 136 141













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443					448					453					458	
gaa	tgt	gga	aaa	gcc	ttt	cgt	ctt	caa	gga	gaa	ctt	acc	cga	cat	cac	1622
Glu	Cys	Gly	Lys	Ala	Phe	Arg	Leu	Gln	Gly	Glu	Leu	Thr	Arg	His	His	
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aga	att	cat	aca	tgt	gag	aaa	ccc	tat	gaa	tgt	aag	gaa	tgt	ggg	aag	1670
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gct	ttt	att	cat	agc	aat	caa	ttt	att	tca	cac	cag	cga	att	cac	acc	1718
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Ser	Glu	Ser	Thr	Tyr	Ile	Cys	Lys	Glu	Cys	Gly	Lys	Ile	Phe	Ser	Arg	
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cgc	tat	aat	ctt	act	caa	cat	ttt	aaa	att	cat	act	ggt	gaa	aaa	ccc	1814
Arg	Tyr	Asn	Leu	Thr	Gln	His	Phe	Lys	Ile	His	Thr	Gly	Glu	Lys	Pro	
523					528					533					538	
tac	ata	tgt	aat	gaa	tgt	ggg	aaa	gcc	ttt	cga	ttt	caa	aca	gaa	ctt	1862
Tyr	Ile	Cys	Asn	Glu	Cys	Gly	Lys	Ala	Phe	Arg	Phe	Gln	Thr	Glu	Leu	
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act	cag	cat	cac	aga	att	cat	act	ggt	gaa	aaa	ccc	tat	aaa	tgt	aca	1910
Thr	Gln	His	His	Arg	Ile	His	Thr	Gly	Glu	Lys	Pro	Tyr	Lys	Cys	Thr	
555					560					565					570	
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Arg	Ile	His	Thr	Gly	Glu	Lys	Pro	Tyr	Glu	Cys	Thr	Glu	Cys	Gly	Lys	
587					592					597					602	
acg	ttt	agt	cgg	cac	tat	cat	ctt	act	caa	cat	cac	aga	ggc	cat	act	2054
Thr	Phe	Ser	Arg	His	Tyr	His	Leu	Thr	Gln	His	His	Arg	Gly	His	Thr	
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ggt	gag	aag	ccc	tac	ata	tgt	aat	gaa	tgt	ggg	aat	gct	ttt	att	tgc	2102
Gly	Glu	Lys	Pro	Tyr	Ile	Cys	Asn	Glu	Cys	Gly	Asn	Ala	Phe	Ile	Cys	
619					624					629					634	
agt	tat	cga	ctt	aca	tta	cat	caa	aga	att	cac	act	ggt	gag	ctt	cca	2150
Ser	Tyr	Arg	Leu	Thr	Leu	His	Gln	Arg	Ile	His	Thr	Gly	Glu	Leu	Pro	
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Tyr	Glu	Cys	Lys	Glu	Cys	Gly	Lys	Thr	Phe	Ser	Arg	Arg	Tyr	His	Leu	
651					656					661					666	



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Thr Ala Gln Val Gly Ile Thr Met Pro Arg Thr Lys Ala Ser Ala Pro				
41	46	51	56	
gca ggc gca ctg aag acc cca gga act ggt aag agg ccg ggg ctg tct				423
Ala Gly Ala Leu Lys Thr Pro Gly Thr Gly Lys Arg Pro Gly Leu Ser				
57	62	67	72	
tgg ccc tgg ggc acc aac gcc agc agc tcc tcc gca gtt agc aag gat				471
Trp Pro Trp Gly Thr Asn Ala Ser Ser Ser Ser Ala Val Ser Lys Asp				
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ggc ctg ggc ttt cag tct gtc agc agc ctc cac acc agc tgt gag tcc				519
Gly Leu Gly Phe Gln Ser Val Ser Ser Leu His Thr Ser Cys Glu Ser				
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atc gac atc tcc ctc agc agt gga ggg gtc ccc agc cac aat tct tcc				567
Ile Asp Ile Ser Leu Ser Ser Gly Gly Val Pro Ser His Asn Ser Ser				
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act ggc ctc atc gcc tcc tcc aag gac gac tcc ttg act ccc ttt gtc				615
Thr Gly Leu Ile Ala Ser Ser Lys Asp Asp Ser Leu Thr Pro Phe Val				
121	126	131	136	
aga act aac agt gtg aag acc aca ctg tca gaa agg ttg gtg ctg tgc				663
Arg Thr Asn Ser Val Lys Thr Thr Leu Ser Glu Arg Leu Val Leu Cys				
137	142	147	152	
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Leu Trp Leu Pro Phe Ser Glu Arg His Pro Ser Lys Asn Lys Lys Ile				
153	158	163	168	
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Pro Glu Ala Gly Val Cys Ser Leu Ala Leu Pro Ser Asp Leu Gln Leu
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Asp Arg Arg Gly Ala Glu Gly Pro Glu Ala Glu Arg Leu Arg Ala Ala
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Pro Arg His Asn Gly Ala Ala Glu Pro Glu Pro Glu Ala Glu Thr Ala	
61 66 71 76	
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93 98 103 108	
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Ile Ala Lys Pro Ala Tyr Ser Pro Ala Ser Trp Ser Ser Arg Ser Ala	
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Val Asp Leu Ser Cys Ser Arg Arg Leu Ser Ser Ala His Asn Gly Gly	
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Ser Ala Phe Gly Ala Ala Gly Tyr Gly Gly Ala Gln Pro Thr Pro Pro	
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Arg Ala Asp Tyr Asp Thr Leu Ser Leu Arg Ser Leu Arg Leu Gly Pro	
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189 194 199 204	
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Ala Ala Thr Ser Thr Tyr Arg Ala Phe Ala Tyr Glu Arg Gln Ala Ser	
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Gly 269	Ala	Val	Leu	Glu	Pro 274	Val	Ala	Arg	Ala	Pro 279	Ser	Val	Arg	Ser	Leu 284	
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Ser Ile Asn His Ala Leu Asp Ala Gly Lys Cys Glu Asp Lys Ser Val							
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Glu Asn Ala Val Cys Val Leu Arg Asn Leu Ser Tyr Arg Leu Tyr Asp							
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Glu Met Pro Pro Ser Ala Leu Gln Arg Leu Glu Gly Arg Gly Arg Arg							
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Gln Ser Arg Arg Leu Arg Glu Leu Pro Leu Ala Ala Asp Ala Leu Thr							
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Asn Ala Arg Asn Lys Asp Glu Met Ser Thr Lys Val Val Ser His Leu							
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His Arg Asp Phe Arg Ala Lys Gly Tyr Arg Lys Glu Asp Phe Leu Gly	
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Pro *	
797	

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Gly Arg Gly Ile Ser Phe Ile Phe Cys Cys Phe Arg Asn Asn Asp His						
8 13 18 23						
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Pro Glu Ile Thr Tyr Arg Leu Arg Asn Asp Ser Asn Phe Ala Leu Gln						
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Thr Met Glu Pro Ala Leu Pro Met Pro Pro Val Glu Glu Leu Asp Val						
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Met Phe Ser Glu Leu Val Asp Glu Leu Asp Leu Thr Asp Lys His Arg						
56 61 66 71						
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Glu Ala Met Phe Ala Leu Pro Ala Glu Lys Lys Trp Gln Ile Tyr Cys						
72 77 82 87						
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Ser Lys Lys Lys Asp Gln Glu Glu Asn Lys Gly Ala Thr Ser Trp Pro						
88 93 98 103						
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Glu Phe Tyr Ile Asp Gln Leu Asn Ser Met Ala Ala Arg Lys Ser Leu						
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Gly Arg Arg Ala Gln	Asn Cys Asn Ile Leu	Leu Ser Arg Leu Lys	Leu				
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696	701	706	711				
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Ile Asp Lys Asn Ile	Thr Leu Leu His Tyr	Leu Ile Thr Ile Val	Glu				
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Ser	Ala	Ala	Arg	Thr	Arg	Leu	Phe	Leu	Ala	Ser	Leu	Pro	Gly	Ser	Thr	
939					944					949					954	
cac	tct	acc	gct	gct	gag	ctc	acc	gga	ccc	agc	ctg	gtg	gaa	gtg	ctc	3050
His	Ser	Thr	Ala	Ala	Glu	Leu	Thr	Gly	Pro	Ser	Leu	Val	Glu	Val	Leu	
955					960					965					970	
aga	gcc	aga	ccc	tgg	ttt	gag	gag	ccc	ccc	aag	gct	gtg	gaa	ctg	gag	3098
Arg	Ala	Arg	Pro	Trp	Phe	Glu	Glu	Pro	Pro	Lys	Ala	Val	Glu	Leu	Glu	
971					976					981					986	
ggg	ttg	gcg	gcc	tgt	gag	ggc	gag	tac	tcc	caa	aag	tac	agt	acc	atg	3146
Gly	Leu	Ala	Ala	Cys	Glu	Gly	Glu	Tyr	Ser	Gln	Lys	Tyr	Ser	Thr	Met	
987					992					997					1002	
agc	ccg	ctg	ggc	agt	ggg	gcc	ttc	ggc	ttc	gtg	tgg	act	gct	gtg	gac	3194
Ser	Pro	Leu	Gly	Ser	Gly	Ala	Phe	Gly	Phe	Val	Trp	Thr	Ala	Val	Asp	

1003		1008		1013		1018	
aag gaa aaa aac aag gag	gtg gtg gtg aag ttt	att aag aag gag aag	3242				
Lys Glu Lys Asn Lys Glu	Val Val Val Lys Phe	Ile Lys Lys Glu Lys					
1019	1024	1029	1034				
gtc ttg gag gat tgt tgg	att gag gat ccc aaa	ctt ggg aaa gtt act	3290				
Val Leu Glu Asp Cys Trp	Ile Glu Asp Pro Lys	Leu Gly Lys Val Thr					
1035	1040	1045	1050				
tta gag atc gca att cta	tcc agg gtg gag cac	gcc aat atc atc aag	3338				
Leu Glu Ile Ala Ile Leu	Ser Arg Val Glu His	Ala Asn Ile Ile Lys					
1051	1056	1061	1066				
gta ttg gat ata ttt gaa	aac caa ggg ttc ttc	cag ctt gtg atg gag	3386				
Val Leu Asp Ile Phe Glu	Asn Gln Gly Phe Phe	Gln Leu Val Met Glu					
1067	1072	1077	1082				
aag cac ggc tcc ggc cta	gac ctc ttc gct ttc	atc gac cgc cac ccc	3434				
Lys His Gly Ser Gly Leu	Asp Leu Phe Ala Phe	Ile Asp Arg His Pro					
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agg ctg gat gag ccc ctg	gcg agc tac atc ttc	cga caa gtg aga gca	3482				
Arg Leu Asp Glu Pro Leu	Ala Ser Tyr Ile Phe	Arg Gln Val Arg Ala					
1099	1104	1109	1114				
ggc cag agc cgt cta gtg	tca gca gtg gga tac	ctg cgc ttg aag gac	3530				
Gly Gln Ser Arg Leu Val	Ser Ala Val Gly Tyr	Leu Arg Leu Lys Asp					
1115	1120	1125	1130				
atc atc cac cgt gac atc	aag gat gag aac atc	gtg atc gct gag gac	3578				
Ile Ile His Arg Asp Ile	Lys Asp Glu Asn Ile	Val Ile Ala Glu Asp					
1131	1136	1141	1146				
ttc aca atc aag ctg ata	gac ttt ggc tcg gcc	gcc tac ttg gaa agg	3626				
Phe Thr Ile Lys Leu Ile	Asp Phe Gly Ser Ala	Ala Tyr Leu Glu Arg					
1147	1152	1157	1162				
gga aaa tta ttt tat act	ttt tgt ggg acc atc	gag tac tgt gca ccg	3674				
Gly Lys Leu Phe Tyr Thr	Phe Cys Gly Thr Ile	Glu Tyr Cys Ala Pro					
1163	1168	1173	1178				
gaa gtt ctc atg ggg aat	ccc tac aga ggg ccg	gag ctg gag atg tgg	3722				
Glu Val Leu Met Gly Asn	Pro Tyr Arg Gly Pro	Glu Leu Glu Met Trp					
1179	1184	1189	1194				
tct ctg gga gtc act ctg	tac acg ctg gtc ttt	gag gag aac ccc ttc	3770				
Ser Leu Gly Val Thr Leu	Tyr Thr Leu Val Phe	Glu Glu Asn Pro Phe					
1195	1200	1205	1210				
tgt gag ctg gag gag acc	gtg gag gct gcc ata	cac ccg cca tac ctg	3818				
Cys Glu Leu Glu Glu Thr	Val Glu Ala Ala Ile	His Pro Pro Tyr Leu					
1211	1216	1221	1226				
gtg tcc aaa gaa ctc atg	agc ctt gtg tct ggg	ctg ctg cag cca gtc	3866				
Val Ser Lys Glu Leu Met	Ser Leu Val Ser Gly	Leu Leu Gln Pro Val					
1227	1232	1237	1242				



Glu	Asp	Gln	Arg	Cys	Leu	Ser	Gln	Ser	Leu	Pro	Leu	Pro	Val	Ser	Ala	
11					16					21					26	
gag	ggc	cca	gct	gca	cag	acc	act	gct	gag	ccc	agc	agg	tcg	ttt	tcc	266
Glu	Gly	Pro	Ala	Ala	Gln	Thr	Thr	Ala	Glu	Pro	Ser	Arg	Ser	Phe	Ser	
27					32					37					42	
tca	gcc	cac	aga	cac	ctg	agc	aga	agg	aat	ggg	ctt	tcc	aga	ctc	tgc	314
Ser	Ala	His	Arg	His	Leu	Ser	Arg	Arg	Asn	Gly	Leu	Ser	Arg	Leu	Cys	
43					48					53					58	
cag	agc	agg	aca	gcg	ctc	tct	gaa	gac	aga	tgg	agc	tcc	tat	tgt	cta	362
Gln	Ser	Arg	Thr	Ala	Leu	Ser	Glu	Asp	Arg	Trp	Ser	Ser	Tyr	Cys	Leu	
59					64					69					74	
tca	tca	ctg	gct	gcc	cag	aat	att	tgt	aca	agt	aaa	ctg	cac	tgc	cct	410
Ser	Ser	Leu	Ala	Ala	Gln	Asn	Ile	Cys	Thr	Ser	Lys	Leu	His	Cys	Pro	
75					80					85					90	
gct	gcc	cct	gag	cac	acg	gac	ccg	tcc	gaa	ccg	cgg	ggc	agt	gtg	tcc	458
Ala	Ala	Pro	Glu	His	Thr	Asp	Pro	Ser	Glu	Pro	Arg	Gly	Ser	Val	Ser	
91					96					101					106	
tgc	tgc	tcc	ctg	ctg	cgg	gga	ctg	tcc	tca	ggg	tgg	tcc	tca	cct	ctg	506
Cys	Cys	Ser	Leu	Leu	Arg	Gly	Leu	Ser	Ser	Gly	Trp	Ser	Ser	Pro	Leu	
107					112					117					122	
ctt	ccg	gcc	cct	gtg	tgc	aac	cct	aac	aag	gcc	atc	ttc	acg	gtg	gat	554
Leu	Pro	Ala	Pro	Val	Cys	Asn	Pro	Asn	Lys	Ala	Ile	Phe	Thr	Val	Asp	
123					128					133					138	
gcc	aag	acc	aca	gag	atc	ctc	gtt	gct	aac	gac	aaa	gct	tgc	ggg	ctc	602
Ala	Lys	Thr	Thr	Glu	Ile	Leu	Val	Ala	Asn	Asp	Lys	Ala	Cys	Gly	Leu	
139					144					149					154	
ctg	ggg	tac	agc	agc	cag	gac	ctg	att	ggc	cag	aag	ctc	acg	cag	ttc	650
Leu	Gly	Tyr	Ser	Ser	Gln	Asp	Leu	Ile	Gly	Gln	Lys	Leu	Thr	Gln	Phe	
155					160					165					170	
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Phe	Leu	Arg	Ser	Asp	Ser	Asp	Val	Val	Glu	Ala	Leu	Ser	Glu	Glu	His	
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Met	Glu	Ala	Asp	Gly	His	Ala	Ala	Val	Val	Phe	Gly	Thr	Val	Val	Asp	
187					192					197					202	
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Ile	Ile	Ser	Arg	Ser	Gly	Glu	Lys	Ile	Pro	Val	Ser	Val	Trp	Met	Lys	
203					208					213					218	
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Arg	Met	Arg	Gln	Glu	Arg	Arg	Leu	Cys	Cys	Val	Val	Val	Leu	Glu	Pro	
219					224					229					234	
gtg	gag	agg	gtc	tcg	acc	tgg	gtc	gct	ttc	cag	agc	gat	ggc	acc	gtc	890
Val	Glu	Arg	Val	Ser	Thr	Trp	Val	Ala	Phe	Gln	Ser	Asp	Gly	Thr	Val	











1147	1152	1157	1162	
tgt ggg acc atc gag tac	tgt gca ccg gaa gtt	ctc atg ggg aat ccc	3674	
Cys Gly Thr Ile Glu Tyr	Cys Ala Pro Glu Val	Leu Met Gly Asn Pro		
1163	1168	1173	1178	
tac aga ggg ccg gag ctg	gag atg tgg tct ctg	gga gtc act ctg tac	3722	
Tyr Arg Gly Pro Glu Leu	Glu Met Trp Ser Leu	Gly Val Thr Leu Tyr		
1179	1184	1189	1194	
acg ctg gtc ttt gag gag	aac ccc ttc tgt gag	ctg gag gag acc gtg	3770	
Thr Leu Val Phe Glu Glu	Asn Pro Phe Cys Glu	Leu Glu Glu Thr Val		
1195	1200	1205	1210	
gag gct gcc ata cac ccg	cca tac ctg gtg tcc	aaa gaa ctc atg agc	3818	
Glu Ala Ala Ile His Pro	Pro Tyr Leu Val Ser	Lys Glu Leu Met Ser		
1211	1216	1221	1226	
ctt gtg tct ggg ctg ctg	cag cca gtc cct gag	aga cgc acc acc ttg	3866	
Leu Val Ser Gly Leu Leu	Gln Pro Val Pro Glu	Arg Arg Thr Thr Leu		
1227	1232	1237	1242	
gag aag ctg gtg aca gac	ccg tgg gta aca cag	cct gtg aat ctt gct	3914	
Glu Lys Leu Val Thr Asp	Pro Trp Val Thr Gln	Pro Val Asn Leu Ala		
1243	1248	1253	1258	
gac tat aca tgg gaa gag	gtg ttt cga gta aac	aag cca gaa agt gga	3962	
Asp Tyr Thr Trp Glu Glu	Val Phe Arg Val Asn	Lys Pro Glu Ser Gly		
1259	1264	1269	1274	
gtt ctg tcc gct gcg agc	ctg gag atg ggg aac	agg agc ctg agt gat	4010	
Val Leu Ser Ala Ala Ser	Leu Glu Met Gly Asn	Arg Ser Leu Ser Asp		
1275	1280	1285	1290	
gtg gcc cag gct cag gag	ctt tgt ggg ggc ccc	gtt cca ggc gag gct	4058	
Val Ala Gln Ala Gln Glu	Leu Cys Gly Gly Pro	Val Pro Gly Glu Ala		
1291	1296	1301	1306	
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Pro Asn Gly Gln Gly Cys	Leu His Pro Gly Asp	Pro Arg Leu Leu Thr		
1307	1312	1317	1322	
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Ser *				
1323				
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gatttattac atagatttgg	aattcacttt tttcatgacc	tagaaaaaaa cattccagtg	4342	
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 <212> DNA  
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 <222> (402)..(2069)

<400> 144

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gcagtagtct cctcgtttctc cgccgccgct agcctagctg agtcgccggc ttctgcgcta      180
ggggctccca ccgcctccgc aggctaagga gccgctgcca ccaacgagct gtgaggggta      240
ctatgctccc tctttgccgc cgtctcctcc tcttgccccg gcaggcaccc ctctggctgc      300
tcagtcctgc ctcagtgtca aaccagaaga gaagtaaaat tcaacaaaaa tttatgtgtg      360
gagttccttc ttaaaagaag aaaaaagtga ttatttagac t      atg gat cgg agc      413
                               Met Asp Arg Ser
                               1

aaa cgg aat tca att gca gga ttt cct cca cgt gtg gag cgt ctt gaa      461
Lys Arg Asn Ser Ile Ala Gly Phe Pro Pro Arg Val Glu Arg Leu Glu
   5                10                15                20

gag ttt gaa gga ggt ggt gga gga gaa gga aat gtg agc cag gtg gga      509
Glu Phe Glu Gly Gly Gly Gly Gly Glu Gly Asn Val Ser Gln Val Gly
  21                26                31                36

aga gtt tgg cca tct tcg tat cga gct ctt ata agt gcc ttt tcc aga      557
Arg Val Trp Pro Ser Ser Tyr Arg Ala Leu Ile Ser Ala Phe Ser Arg
  37                42                47                52

ctg acg cgt ttg gat gat ttc acc tgt gaa aaa ata ggg tct ggc ttc      605
Leu Thr Arg Leu Asp Asp Phe Thr Cys Glu Lys Ile Gly Ser Gly Phe
  53                58                63                68

ttt tct gaa gtg ttc aag gta cga cac cga gct tct ggt cag gtg atg      653
Phe Ser Glu Val Phe Lys Val Arg His Arg Ala Ser Gly Gln Val Met
  69                74                79                84

gct ctt aag atg aac aca ttg agc agt aac cgg gca aac atg ctg aaa      701
Ala Leu Lys Met Asn Thr Leu Ser Ser Asn Arg Ala Asn Met Leu Lys
  85                90                95                100

gaa gta cag ctc atg aat aga ctc tcc cat ccc aac atc ctt agg tat      749
Glu Val Gln Leu Met Asn Arg Leu Ser His Pro Asn Ile Leu Arg Tyr
 101                106                111                116

atc aac tcc ggg aac ctg gaa cag ttg cta gac agt aac ctg cat ttg      797
Ile Asn Ser Gly Asn Leu Glu Gln Leu Leu Asp Ser Asn Leu His Leu
 117                122                127                132

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ccaagcctct gaaatccagc aaggaggtct gcctcccacc agaccctctc cagtgtactt 2339
ccccagatag gaccagagga tgtctagtct taggctgagc tggcaggcag ctattacccc 2399
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<210> 145
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<220>
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<222> (402) .. (1985)

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gcagtagtct cctcgttctc cgccgccgct agcctagctg agtcgccggc ttctgcgcta 180
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ctatgctccc tctttgccgc cgtctcctcc tcttgccgc gcaggcacc ctctggctgc 300
tcagtcctgc ctcagtgtca aaccagaaga gaagtaaaat tcaacaaaaa tttatgtgtg 360
gagttccttc ttaaaagaag aaaaaagtga ttatttagac t      atg gat cgg agc 413
                                Met Asp Arg Ser
                                1
aaa cgg aat tca att gca gga ttt cct cca cgt gtg gag cgt ctt gaa 461

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Lys	Arg	Asn	Ser	Ile	Ala	Gly	Phe	Pro	Pro	Arg	Val	Glu	Arg	Leu	Glu	
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Glu	Phe	Glu	Gly	Gly	Gly	Gly	Gly	Glu	Gly	Asn	Val	Ser	Gln	Val	Gly	
21					26					31					36	
aga	gtt	tgg	cca	tct	tcg	tat	cga	gct	ctt	ata	agt	gcc	ttt	tcc	aga	557
Arg	Val	Trp	Pro	Ser	Ser	Tyr	Arg	Ala	Leu	Ile	Ser	Ala	Phe	Ser	Arg	
37					42					47					52	
ctg	acg	cgt	ttg	gat	gat	ttc	acc	tgt	gaa	aaa	ata	ggg	tct	ggc	ttc	605
Leu	Thr	Arg	Leu	Asp	Asp	Phe	Thr	Cys	Glu	Lys	Ile	Gly	Ser	Gly	Phe	
53					58					63					68	
ttt	tct	gaa	gtg	ttc	aag	gta	cga	cac	cga	gct	tct	ggg	cag	gtg	atg	653
Phe	Ser	Glu	Val	Phe	Lys	Val	Arg	His	Arg	Ala	Ser	Gly	Gln	Val	Met	
69					74					79					84	
gct	ctt	aag	atg	aac	aca	ttg	agc	agt	aac	cgg	gca	aac	atg	ctg	aaa	701
Ala	Leu	Lys	Met	Asn	Thr	Leu	Ser	Ser	Asn	Arg	Ala	Asn	Met	Leu	Lys	
85					90					95					100	
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Glu	Val	Gln	Leu	Met	Asn	Arg	Leu	Ser	His	Pro	Asn	Ile	Leu	Arg	Tyr	
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Pro	Trp	Thr	Val	Arg	Val	Lys	Leu	Ala	Tyr	Asp	Ile	Ala	Val	Gly	Leu	
133					138					143					148	
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Ser	Tyr	Leu	His	Phe	Lys	Gly	Ile	Phe	His	Arg	Asp	Leu	Thr	Ser	Lys	
149					154					159					164	
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Asn	Cys	Leu	Ile	Lys	Arg	Asp	Glu	Asn	Gly	Tyr	Ser	Ala	Val	Val	Ala	
165					170					175					180	
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Lys	Leu	Ala	Val	Val	Gly	Ser	Pro	Phe	Trp	Met	Ala	Pro	Glu	Val	Leu	
197					202					207					212	
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Arg	Asp	Glu	Pro	Tyr	Asn	Glu	Lys	Asn	Phe	Gly	Leu	Asp	Tyr	Asp	Ala	
213					218					223					228	
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Phe	Gln	His	Met	Val	Gly	Asp	Cys	Pro	Pro	Asp	Phe	Leu	Gln	Leu	Thr	





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cag ggg acc agt cca tgc cct gcg ggt gct tct gag gag atg gag gta	1901
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485 490 495 500	
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Glu Glu Arg Pro Ala Gly Ser Thr Pro Ala Thr Phe Ser Thr Ser Gly	
501 506 511 516	
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Ile Gly Leu Gln Thr Gln Gly Lys Gln Asp Gly *	
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<220>

<221> CDS

<222> (55) .. (957)

<400> 146

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gac	tct	gac	tct	tgc	gcc	gcc	105
Asp	Ser	Asp	Ser	Cys	Ala	Ala	
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agt	tgc	aag	agg	cgc	agg	acc	153
Ser	Cys	Lys	Arg	Arg	Arg	Thr	
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ttt	gtc	ttg	gcc	tat	gct	ggc	201
Phe	Val	Leu	Ala	Tyr	Ala	Gly	
34					39	44	49
cct	tta	agg	agc	agc	ccc	agc	249
Pro	Leu	Arg	Ser	Ser	Pro	Ser	
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gac	agc	gac	ggc	tgg	gac	gcg	297
Asp	Ser	Asp	Gly	Trp	Asp	Ala	
66					71	76	81
ccc	ttg	cca	gtc	tct	gac	cgc	345
Pro	Leu	Pro	Val	Ser	Asp	Arg	
82					87	92	97
ttg	cag	cga	gcc	aag	ccc	agt	393
Leu	Gln	Arg	Ala	Lys	Pro	Ser	
98					103	108	113
gac	aag	ctg	aag	aag	aag	aag	441
Asp	Lys	Leu	Lys	Lys	Lys	Lys	
114					119	124	129
cct	ggg	aaa	gag	ggg	tac	agg	489
Pro	Gly	Lys	Glu	Gly	Tyr	Arg	
130					135	140	145
gac	ccc	tac	gtg	gag	acc	ccc	537
Asp	Pro	Tyr	Val	Glu	Thr	Pro	
146					151	156	161
cag	gct	ccc	agc	gac	ccc	tgc	585
Gln	Ala	Pro	Ser	Asp	Pro	Cys	
162					167	172	177
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<213> Homo sapiens

<220>

<221> CDS

<222> (673)..(2616)

<400> 147

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		Met Pro Val Ser Leu Glu Asp Ser Gly Glu Pro Thr				
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Ser Cys Pro Ala Thr Asp Ala Glu Thr Ala Ser Glu Gly Ser Val Glu						
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Ser Ala Ser Glu Thr Arg Ser Gly Pro Gln Ser Ala Ser Thr Ala Val						
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Lys Glu Arg Pro Ala Ser Ser Glu Lys Val Lys Gly Gly Asp Asp His						
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Gln Asn Arg Leu Arg Arg Lys Arg Glu Gln Glu Pro Thr Glu Arg Pro						
77 82 87 92						
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Leu Lys Gly Ile Gln Ser Arg Leu Arg Lys Lys Arg Arg Glu Glu Gly						
93 98 103 108						







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Pro Val Val Pro Ser Val Pro Met Ala Ser Pro Ala Pro Gly Arg Leu				
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Gly Ala Met Ser Ala Ala Pro Ser Gln Pro Asn Ser Gln Ile Arg Gln				
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Asn Ile Arg Arg Ser Leu Lys Glu Ile Leu Trp Lys Ser Ser Phe Phe				
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Leu Phe Cys Ser Glu Ser Met Thr Ala Met Thr *				
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actaagcaaa atg agg cgg ttc ctg agg cca ggg cat gac cct gtg cgg 169
          Met Arg Arg Phe Leu Arg Pro Gly His Asp Pro Val Arg
              1              5              10

gag agg ctc aag cgg gac ctg ttc cag ttt aac aag acg gtg gag cat 217
Glu Arg Leu Lys Arg Asp Leu Phe Gln Phe Asn Lys Thr Val Glu His
 14              19              24              29

ggc ttc ccg cac cag ccc agc gcc ctc ggc tac agc ccg tcc ctg cgc 265
Gly Phe Pro His Gln Pro Ser Ala Leu Gly Tyr Ser Pro Ser Leu Arg
 30              35              40              45

atc ctg gcc atc ggc acc cgt tct gga gcc atc aag ctc tac gga gcc 313
Ile Leu Ala Ile Gly Thr Arg Ser Gly Ala Ile Lys Leu Tyr Gly Ala
 46              51              56              61

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cag atc cac ctc ctg ccc ggc cag tgc cag ctg gtc acc ctg ctg gat	409
Gln Ile His Leu Leu Pro Gly Gln Cys Gln Leu Val Thr Leu Leu Asp	
78 83 88 93	
gac aac agc ctg cac ctt tgg agc ctg aag gtc aag ggc ggg gca tcg	457
Asp Asn Ser Leu His Leu Trp Ser Leu Lys Val Lys Gly Gly Ala Ser	
94 99 104 109	
gag ctg cag gag gat gag agc ttc aca ctg cgt gga ccc cca ggg gct	505
Glu Leu Gln Glu Asp Glu Ser Phe Thr Leu Arg Gly Pro Pro Gly Ala	
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gcc ccc agt gcc aca cag atc acc gtg gtc ctg cca cat tcc tcc tgc	553
Ala Pro Ser Ala Thr Gln Ile Thr Val Val Leu Pro His Ser Ser Cys	
126 131 136 141	
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Glu Leu Leu Tyr Leu Gly Thr Glu Ser Gly Asn Val Phe Val Val Gln	
142 147 152 157	
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Leu Pro Ala Phe Arg Ala Leu Glu Asp Arg Thr Ile Ser Ser Asp Ala	
158 163 168 173	
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Val Leu Gln Arg Leu Pro Glu Glu Ala Arg His Arg Arg Val Phe Glu	
174 179 184 189	
atg gtg gag gca ctg cag gag cac cct cga gac ccc aac cag atc ctg	745
Met Val Glu Ala Leu Gln Glu His Pro Arg Asp Pro Asn Gln Ile Leu	
190 195 200 205	
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Ile Gly Tyr Ser Arg Gly Leu Val Val Ile Trp Asp Leu Gln Gly Ser	
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Arg Val Leu Tyr His Phe Leu Ser Ser Gln Gln Leu Glu Asn Ile Trp	
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Trp Gln Arg Asp Gly Arg Leu Leu Val Ser Cys His Ser Asp Gly Ser	
238 243 248 253	
tac tgc cag tgg ccc gtg tcc agc gaa gcc cag caa cca gag ccc ctc	937
Tyr Cys Gln Trp Pro Val Ser Ser Glu Ala Gln Gln Pro Glu Pro Leu	
254 259 264 269	
cgc agc ctc gtg cct tac ggt ccc ttt cct tgc aaa gcg att acc aga	985
Arg Ser Leu Val Pro Tyr Gly Pro Phe Pro Cys Lys Ala Ile Thr Arg	
270 275 280 285	



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Gly	Gln	Val	Leu	Val	Leu	Glu	Leu	Asn	Asp	Glu	Ala	Ala	Glu	Gln	Ala	
526					531					536					541	
gtg	gag	cag	gtg	gag	gcc	gac	ctg	ctg	cag	gac	caa	gag	ggc	tac	cgc	1801
Val	Glu	Gln	Val	Glu	Ala	Asp	Leu	Leu	Gln	Asp	Gln	Glu	Gly	Tyr	Arg	
542					547					552					557	
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Trp	Lys	Gly	His	Glu	Arg	Leu	Ala	Ala	Arg	Ser	Gly	Pro	Val	Arg	Phe	
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Glu	Pro	Gly	Phe	Gln	Pro	Phe	Val	Leu	Val	Gln	Cys	Gln	Pro	Pro	Ala	
574					579					584					589	
gtg	gtc	acc	tcc	ttg	gcc	ctg	cac	tct	gag	tgg	cgg	ctc	gtg	gcc	ttc	1945
Val	Val	Thr	Ser	Leu	Ala	Leu	His	Ser	Glu	Trp	Arg	Leu	Val	Ala	Phe	
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Gly	Thr	Ser	His	Gly	Phe	Gly	Leu	Phe	Asp	His	Gln	Gln	Arg	Arg	Gln	
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gtc	ttt	gtt	aag	tgc	aca	ctg	cac	ccc	agt	gac	cag	ctg	gcc	ttg	gag	2041
Val	Phe	Val	Lys	Cys	Thr	Leu	His	Pro	Ser	Asp	Gln	Leu	Ala	Leu	Glu	
622					627					632					637	
ggc	cca	ctc	tcc	cgc	gtc	aag	tcc	ctc	aag	aag	tcc	ttg	cgt	cag	tca	2089
Gly	Pro	Leu	Ser	Arg	Val	Lys	Ser	Leu	Lys	Lys	Ser	Leu	Arg	Gln	Ser	
638					643					648					653	
ttc	cgc	cgg	atg	cgt	cgg	agc	cgg	gtg	tcc	agc	cgg	aag	cgg	cac	ccg	2137
Phe	Arg	Arg	Met	Arg	Arg	Ser	Arg	Val	Ser	Ser	Arg	Lys	Arg	His	Pro	
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gct	ggc	ccc	cca	gga	gag	gca	cag	gag	ggg	agt	gcc	aag	gct	gag	cgg	2185
Ala	Gly	Pro	Pro	Gly	Glu	Ala	Gln	Glu	Gly	Ser	Ala	Lys	Ala	Glu	Arg	
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cca	ggc	ctc	cag	aac	atg	gag	ctg	gcg	cct	gtg	cag	cgc	aag	atc	gag	2233
Pro	Gly	Leu	Gln	Asn	Met	Glu	Leu	Ala	Pro	Val	Gln	Arg	Lys	Ile	Glu	
686					691					696					701	
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Ala	Arg	Ser	Ala	Glu	Asp	Ser	Phe	Thr	Gly	Phe	Val	Arg	Thr	Leu	Tyr	
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Phe	Ala	Asp	Thr	Tyr	Leu	Lys	Asp	Ser	Ser	Arg	His	Cys	Pro	Ser	Leu	
718					723					728					733	
tgg	gct	ggc	acc	aat	ggg	ggc	acc	atc	tat	gcc	ttc	tcc	ctg	cgt	gtg	2377
Trp	Ala	Gly	Thr	Asn	Gly	Gly	Thr	Ile	Tyr	Ala	Phe	Ser	Leu	Arg	Val	





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Val His Ile Glu Pro Pro Trp Gly Ala Ala Ser Ala Met Ala Glu Gln	
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actaagcaaa atg agg cgg ttc ctg agg cca ggg cat gac cct gtg cgg	169
Met Arg Arg Phe Leu Arg Pro Gly His Asp Pro Val Arg	
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gag agg ctc aag cgg gac ctg ttc cag ttt aac aag acg gtg gag cat	217
Glu Arg Leu Lys Arg Asp Leu Phe Gln Phe Asn Lys Thr Val Glu His	
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Gly Phe Pro His Gln Pro Ser Ala Leu Gly Tyr Ser Pro Ser Leu Arg	
30 35 40 45	
atc ctg gcc atc ggc acc cgt tct gga gcc atc aag ctc tac gga gcc	313
Ile Leu Ala Ile Gly Thr Arg Ser Gly Ala Ile Lys Leu Tyr Gly Ala	
46 51 56 61	
cca ggc gtg gag ttc atg ggg ctg cac cag gag aac aac gct gtg acg	361

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Gln	Ile	His	Leu	Leu	Pro	Gly	Gln	Cys	Gln	Leu	Val	Thr	Leu	Leu	Asp 93	
gac 94	aac	agc	ctg	cac	ctt 99	tgg	agc	ctg	aag	gtc 104	aag	ggc	ggg	gca	tcg	457
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Ala	Ser	Arg	Ala	Gly	Leu	Gly	Ala	Cys	Trp	His	Pro	Gln	Cys	Phe	Val	
202					207					212					217	
tgt	acc	acg	tgc	cag	gaa	ctg	ctg	gtt	gac	ctc	atc	tac	ttc	tac	cat	783
Cys	Thr	Thr	Cys	Gln	Glu	Leu	Leu	Val	Asp	Leu	Ile	Tyr	Phe	Tyr	His	
218					223					228					233	
gtt	ggc	aag	gtc	tac	tgc	ggg	cgt	cac	cat	gcc	gaa	tgc	ctg	cgt	cca	831
Val	Gly	Lys	Val	Tyr	Cys	Gly	Arg	His	His	Ala	Glu	Cys	Leu	Arg	Pro	
234					239					244					249	
cgc	tgc	caa	gcc	tgt	gac	gag	atc	atc	ttc	tcc	cct	gag	tgc	acg	gag	879
Arg	Cys	Gln	Ala	Cys	Asp	Glu	Ile	Ile	Phe	Ser	Pro	Glu	Cys	Thr	Glu	
250					255					260					265	
gct	gag	ggc	cgc	cac	tgg	cac	atg	gat	cac	ttc	tgc	tgc	ttt	gag	tgt	927
Ala	Glu	Gly	Arg	His	Trp	His	Met	Asp	His	Phe	Cys	Cys	Phe	Glu	Cys	



agg gcc ccc agc cgt cgc cgc cac cat cat cat aat cac cat cac cat	1647
Arg Ala Pro Ser Arg Arg Arg His His His His Asn His His His His	
506 511 516 521	
cac aac cgc cac cca agc aga cgt cgc cac tat caa tgt gac gcg gga	1695
His Asn Arg His Pro Ser Arg Arg Arg His Tyr Gln Cys Asp Ala Gly	
522 527 532 537	
tca ggg tca gac tcg gaa tct tgc tcc agc tcg ccc tcc agt tcc agt	1743
Ser Gly Ser Asp Ser Glu Ser Cys Ser Ser Ser Pro Ser Ser Ser Ser	
538 543 548 553	
tcc gaa tca tca gag gat gat ggc ttc ttc cta gga gag cgc atc cct	1791
Ser Glu Ser Ser Glu Asp Asp Gly Phe Phe Leu Gly Glu Arg Ile Pro	
554 559 564 569	
ctg ccc ccg cat ttg tgc agg ccc atg cct gct cag gac act gca atg	1839
Leu Pro Pro His Leu Cys Arg Pro Met Pro Ala Gln Asp Thr Ala Met	
570 575 580 585	
gag acc ttc aac tcc cca tct tta tcg ctc ccc agg gac tct cgc gca	1887
Glu Thr Phe Asn Ser Pro Ser Leu Ser Leu Pro Arg Asp Ser Arg Ala	
586 591 596 601	
ggg atg cct cgt cag gcc cga gac aag aac tgc atc gtg gct tga agg	1935
Gly Met Pro Arg Gln Ala Arg Asp Lys Asn Cys Ile Val Ala *	
602 607 612	
caggccgtcc tggagggggc tccattctcc agtcagagta gatgatgagg cccatgcccc	1995
tcacccccac gccccgcccc tacaacctaa gtcataaatc ctcttctctcc ctcttttaaa	2055
aaaaaaaaa a	2066

<210> 152  
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 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (47) .. (3793)

<400> 152	
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Met Met Thr	
1	
ggc tac aat aat ggt cgc tgt ccc cgg aat tct ctc tac agt gac tgc	103
Gly Tyr Asn Asn Gly Arg Cys Pro Arg Asn Ser Leu Tyr Ser Asp Cys	
4 9 14 19	
att att gag gag aag acg gtg gtc ctg cag aaa aaa gac aat gag ggc	151











Tyr 932	Ala	Asp	Gly	Gln	Ala 937	Phe	Met	Val	Asp	Lys 942	Pro	Pro	Val	Pro	Pro 947	
aag 948	cca	aaa	atg	aag	ccc 953	atc	att	cac	aaa	agc 958	aat	gca	ctt	tat	caa 963	2935
Lys	Pro	Lys	Met	Lys	Pro	Ile	Ile	His	Lys	Ser	Asn	Ala	Leu	Tyr	Gln	
gac 964	gcg	ctc	gtg	gaa	gaa 969	gat	gta	gat	agc	ttt 974	gtt	atc	ccc	ccg	ccc 979	2983
Asp	Ala	Leu	Val	Glu	Glu	Asp	Val	Asp	Ser	Phe	Val	Ile	Pro	Pro	Pro	
gct 980	ccc	ccg	ccc	ccg	ccg 985	ggc	agt	gcc	cag	cct 990	ggg	atg	gcc	aag	gtt 995	3031
Ala	Pro	Pro	Pro	Pro	Pro	Gly	Ser	Ala	Gln	Pro	Gly	Met	Ala	Lys	Val	
ctc 996	cag	cca	agg	acc	tcc 1001	aag	ttg	tgg	ggc	gac 1006	gtc	aca	gag	atc	aaa 1011	3079
Leu	Gln	Pro	Arg	Thr	Ser	Lys	Leu	Trp	Gly	Asp	Val	Thr	Glu	Ile	Lys	
agc 1012	ccg	att	ctc	tca	ggc 1017	cca	aag	gca	aac	gtt 1022	att	agt	gaa	ttg	aac 1027	3127
Ser	Pro	Ile	Leu	Ser	Gly	Pro	Lys	Ala	Asn	Val	Ile	Ser	Glu	Leu	Asn	
tct 1028	atc	cta	cag	caa	atg 1033	aac	cga	gag	aaa	ttg 1038	gca	aag	ccg	ggg	gaa 1043	3175
Ser	Ile	Leu	Gln	Gln	Met	Asn	Arg	Glu	Lys	Leu	Ala	Lys	Pro	Gly	Glu	
gga 1044	ctg	gat	tca	cca	atg 1049	gga	gcc	aag	tcc	gcc 1054	agc	ctc	gct	cca	aga 1059	3223
Gly	Leu	Asp	Ser	Pro	Met	Gly	Ala	Lys	Ser	Ala	Ser	Leu	Ala	Pro	Arg	
agc 1060	ccg	gag	atc	atg	agc 1065	acc	atc	tca	ggt	aca 1070	cgg	agc	acg	acg	gtc 1075	3271
Ser	Pro	Glu	Ile	Met	Ser	Thr	Ile	Ser	Gly	Thr	Arg	Ser	Thr	Thr	Val	
acc 1076	ttc	act	gtt	cgc	ccc 1081	ggc	acc	tcc	cag	ccc 1086	atc	acc	ctg	cag	agc 1091	3319
Thr	Phe	Thr	Val	Arg	Pro	Gly	Thr	Ser	Gln	Pro	Ile	Thr	Leu	Gln	Ser	
cgg 1092	ccc	ccc	gac	tat	gaa 1097	agc	agg	acc	tca	gga 1102	aca	aga	cgt	gcc	cca 1107	3367
Arg	Pro	Pro	Asp	Tyr	Glu	Ser	Arg	Thr	Ser	Gly	Thr	Arg	Arg	Ala	Pro	
agc 1108	cct	gtg	gtc	tcg	cca 1113	aca	gag	atg	aac	aaa 1118	gag	acc	ctg	ccc	gcc 1123	3415
Ser	Pro	Val	Val	Ser	Pro	Thr	Glu	Met	Asn	Lys	Glu	Thr	Leu	Pro	Ala	
ccc 1124	ctg	tct	gct	gcc	acc 1129	gcc	tct	cct	tct	ccc 1134	gct	ctc	tca	gat	gtc 1139	3463
Pro	Leu	Ser	Ala	Ala	Thr	Ala	Ser	Pro	Ser	Pro	Ala	Leu	Ser	Asp	Val	
ttt 1140	agc	ctt	cca	agc	cag 1145	ccc	cct	tct	ggg	gat 1150	cta	ttt	ggc	ttg	aac 1155	3511
Phe	Ser	Leu	Pro	Ser	Gln	Pro	Pro	Ser	Gly	Asp	Leu	Phe	Gly	Leu	Asn	
cca 1140	gcg	gga	cgc	agt	agg 1145	tcg	cca	tcc	ccc	tcg 1150	ata	ctg	caa	cag	cca 1155	3559
Pro	Ala	Gly	Arg	Ser	Arg	Ser	Pro	Ser	Pro	Ser	Ile	Leu	Gln	Gln	Pro	



ccagccaagg	gtgagcatct	ctgctgagac	agtccttttg	ctctcggagg	ccagggaaga	4940
tggtacttag	aggcttttcc	cctatcgctc	tgggtgtcta	ggaatcccac	cagcttgtct	5000
taacagtaca	acagcttctt	tgaggacca	gtgggtatgg	agtatagaca	gaacccaggg	5060
ttgagaacag	aaggtgggcg	gcaggatcag	agtgaagca	gaggcgtgag	gagaggaaag	5120
cagggaggtc	tcctgggctg	ccaggtcagc	ctctctggca	aggctttctt	gagccccgcc	5180
cctttctttc	cccggagtc	ctccacccca	taacaatacc	tcgaatttcc	aaaagaggtc	5240
accagatgca	catgggccgc	aaaacacaca	gtcaggcttc	cagcacattc	tccccattt	5300
ggaggatact	cgaatgtcag	gtttttgggt	ttattattat	ttcagaacta	gctcagccca	5360
tctctaatta	taaaacatgg	ttttgttttt	tttttttcct	ttttttcttg	attaggtctg	5420
gaacagctct	agaatgaaca	cataaaattt	agcaatttaa	aatctttctt	tactgcaagt	5480
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tactaggcag	cctttgtgcc	acttcagtgc	tagaaagtta	aagaaaaaaaa	aacttttgtg	5600
atttaataat	actatttctg	tggaataatt	ataaaagtat	gaccttttta	aatcaacctt	5660
atttgatgc	atctgaacca	gcagagctgt	gttatatttt	ctatctttgc	tagaacttcg	5720
tcattgaagg	acaatttctt	caaagtgggt	acaattcata	atgcagcagt	ttctccaaaa	5780
acaaaaacaa	aacacacacc	acacacacgc	gcttttccag	tcacacaccc	ctgatgttgg	5840
aaccaagttt	ttggaccttc	tgttccaaaa	ccttttgcag	gtcaatcttt	gtatttgaaa	5900
tgatccaatc	caacttgaag	tcaattgaat	attaaggcgc	tttacttccg	tgtgctttca	5960
gtttttccat	catgagatga	atgagcatta	ctctagataa	atttcaagac	aggatactac	6020
aggtggcctg	ctgaggctgc	cccatatttt	agaaaatgta	aaaatgggtg	tttggccatt	6080
aatttgtctt	ccatttgatg	ataccgcaaa	attccgtgag	tccattcctt	tggcatggca	6140
ctttccctgg	gcctacagtt	ggtattacct	ctgtgctcag	tgccaggcaa	aacactagct	6200
caaaggagag	tcaaggaaac	cgctggcaga	cgataaccag	tcgaaactcg	tgacttcggt	6260
ttgttgaact	ttggcagcca	gttgggtgagg	gccagatggt	attccctttc	ttaaagatac	6320
tccaagccac	atgccactaa	ccacaagcaa	gctggctgca	agactaaaga	gctgacaaca	6380
tagtttattt	ttacactgtc	ttattataga	gaagtaatag	acctatcaga	acctgcactg	6440
accaacaaat	aaacacatgt	tgccaagatg	aatcgggtct	tatctctatc	tgcttatttt	6500
ggtactgaaa	gcaatagttc	ctcattcaaa	tcaccaccca	ctgttctccc	cctttgggac	6560

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atgttaggac gaggccctat tccatgcccc tctttaatgg tggaacaaat gttaaactgc 6620
tcatctaaag atcatgttga tattattcca ggttttaaga tcaacttttg ttacatactg 6680
taatttaa ataaactgcatt tacatgccta gtttctgtaa tattgtgtat acaaaaccca 6740
aatctctcaa aatgtaaatt atgtatacct gccaaagatac cttttccagg gtgtctgcgc 6800
acattttaag ttaattcaca taatataaaa attactcaat gtgactgttg atttgctgaa 6860
ctttacatat cacaaagtga attatttgtg atacttttagt taataaaatg gtaaattttt 6920
ttctcagtta ttgaacaagc aagcattatc cagttgatct ggcaatgact ttttgtgtgt 6980
gggccacaat attgattttc ccattaacaa tttttttttg ttttttaaat actaatatgt 7040
ttcacactat agtttgtgta acaacacgtg ttgcgattat ctatgttgct gttacttttg 7100
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<210> 153
<211> 2212
<212> DNA
<213> Homo sapiens

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<220>
<221> CDS
<222> (227) .. (1294)

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ttgagtcatg ctaatagatg gttcaataca tgaatgagtc ccttgctgaa atgctttagg 120
acttcagact accctgaacg ttgattactc tttataactga aataggcatt attcagtgga 180
agagagggaa gaccaaattg atagactgga ctttattcga aaccag atg aac ctt 235
Met Asn Leu
1

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tta aca ctg gat gtt aag aaa aaa atc aag gag gtt acc gag gag gtg 283
Leu Thr Leu Asp Val Lys Lys Lys Ile Lys Glu Val Thr Glu Glu Val
4 9 14 19

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gca aac aaa gtt tca tgt gca atg aca gat gaa att tgt cga ctg tct 331
Ala Asn Lys Val Ser Cys Ala Met Thr Asp Glu Ile Cys Arg Leu Ser
20 25 30 35

```

```

gtt ttg gtt gat gaa ttt tgt tca gag ttt cat cct aat cca gat gta 379
Val Leu Val Asp Glu Phe Cys Ser Glu Phe His Pro Asn Pro Asp Val
36 41 46 51

```

```

tta aaa ata tat aaa agt gaa tta aat aag cac ata gag gat ggt atg 427
Leu Lys Ile Tyr Lys Ser Glu Leu Asn Lys His Ile Glu Asp Gly Met

```



gct cgc ctg tgc caa caa gtt gat att act caa aaa cag ctg gaa gaa	1147
Ala Arg Leu Cys Gln Gln Val Asp Ile Thr Gln Lys Gln Leu Glu Glu	
292 297 302 307	
gaa att gct aga tta ccc aaa gaa ata gat cag ttg gag aaa ata caa	1195
Glu Ile Ala Arg Leu Pro Lys Glu Ile Asp Gln Leu Glu Lys Ile Gln	
308 313 318 323	
aac aat tca aag ctc tta aga aat aaa gct gtt caa ctt gaa aat gag	1243
Asn Asn Ser Lys Leu Leu Arg Asn Lys Ala Val Gln Leu Glu Asn Glu	
324 329 334 339	
ctg gag aat ttt act aag cag ttt cta cct tca agc aat gaa gaa tcc	1291
Leu Glu Asn Phe Thr Lys Gln Phe Leu Pro Ser Ser Asn Glu Glu Ser	
340 345 350 355	
taa caat agagattgct ttggtgacca tgataggagg aaacgaaact tgtaagattg	1348
* 356	
gaacagttgt tatttttatg aaattacttt aaatatgaat tgtactaact gtacctaaat	1408
agcaaagccc tgtgtagatt ctggtaatga tctgtctcag ggtatgtgta tttttgaaga	1468
gtgttatgtc cttagtttta attttgagta aagaaaaggc taaaatcatg aattagttac	1528
aagcaacagt accaacttat gtgacccctg aggggtgggg ctgtgagctc ttaatttggt	1588
tttgattctg aaaaactctg cttcctggca tccaggagtt agagattgag cctttcatct	1648
tctttctcaa aactagtttt tgatgctttc tttcatggga atagtcactt ttttatttag	1708
taaatcgcat tgctggaacc accaaggagt gtggaatgtc cttgagtgtg ttatttatgc	1768
aagtcacagt cacgttgcca tcatggcagc tatgtgaaac actaataaat gtgtttttac	1828
tttttattcc cgttaaaact gatgtaaaac aggataaagg cttggttatag tcacttataa	1888
gtatctgggt ctaagtaatt tccttagatg tttctaaaga aacattttca gctttgctcc	1948
cattatgatt ccaataagga acgctttcct agtgcaattt taggagtaaa gtttgaagag	2008
ataaaaatag ccaaagatag gagacgtctg aattttgaat gataaacagt gatgttttaa	2068
aaaggctggt gttcttcagg aggcatttgc ctaggatatt gctggattat accccattgg	2128
aggcttttaa ttttatttgt atgaattttc caggatttca ttaaaaatta ttattgtatt	2188
ttttacctta aaaaaaaaaa aaaa	2212

<210> 154  
 <211> 2083  
 <212> DNA



<213> Homo sapiens

<220>

<221> CDS

<222> (748)..(1482)

<400> 154

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gtacgtgtgt tttgccc aaa agcaaaatgt gccctcttga gagatgacct ggtgttagta    120
gacagtccag gcacagatgt cactacagag ctggatagct ggattgataa gttttgccta    180
gatgctgatg tctttgtttt ggctcgcaaac tctgaatcaa cactaatgaa tacggaaaaa    240
cacttttttc acaaggtgaa tgagcggcct tccaagccta atattttcat tctcaataat    300
cgttgggatg cctctgcac agagccagaa tatatggaag acgtacgcag acagcacatg    360
gaaagatgcc tgcatttctt ggtggaggag ctcaaagttg taaatgcttt agaagcacag    420
aatcgtatct tctttgtttc agcaaaggaa gttcttagtg ctagaaagca aaaagcacag    480
gggatgccag aaagtgggtg ggcacttgct gaaggatttc atgcaagatt acaggaattt    540
cagaattttg aacaaatctt tgaggagtgt atctcgcagt cagcagtgaa aacaaagttc    600
gaacagcaca ctatcagagc taaacagata ctagctactg tgaaaaacat aatggattca    660
gtaaacctgg cagctgaaga taaaaggcat tattcagtgg aagagagggg agaccaaatt    720
gatagactgg actttattcg aaaccag      atg aac ctt tta aca ctg gat gtt      771
                                Met Asn Leu Leu Thr Leu Asp Val
                                1                               5

aag aaa aaa atc aag gag gtt acc gag gag gtg cca aac aaa gtt tca      819
Lys Lys Lys Ile Lys Glu Val Thr Glu Glu Val Pro Asn Lys Val Ser
  9                               14                               19                               24

tgt gca atg aca gat gaa att tgt cga ctg tct gtt ttg gtt gat gaa      867
Cys Ala Met Thr Asp Glu Ile Cys Arg Leu Ser Val Leu Val Asp Glu
 25                               30                               35                               40

ttt tgt tca gag ttt cat cct aat cca gat gta tta aaa ata tat aaa      915
Phe Cys Ser Glu Phe His Pro Asn Pro Asp Val Leu Lys Ile Tyr Lys
 41                               46                               51                               56

agt ctc cct aga tct tta gct tct act ccc act gct cct acc act cca      963
Ser Leu Pro Arg Ser Leu Ala Ser Thr Pro Thr Ala Pro Thr Thr Pro
 57                               62                               67                               72

gca acg cca gat aat gca tca cag gaa gaa ctc atg att aca tta gta     1011
Ala Thr Pro Asp Asn Ala Ser Gln Glu Glu Leu Met Ile Thr Leu Val
 73                               78                               83                               88

aca gga ttg gcg tcc gtt aca tct aga act tct atg ggc atc att att     1059
Thr Gly Leu Ala Ser Val Thr Ser Arg Thr Ser Met Gly Ile Ile Ile
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<210> 155  
 <211> 3231  
 <212> DNA  
 <213> Homo sapiens  
  
 <220>  
 <221> CDS  
 <222> (331) .. (1158)

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cggctgcgcg ggcttcctgg agtcctgcta ccgcgtcccc gcaggacagt gtgtcaggcg	180
ggcagcttgc cccgccgccc caccggagcg cggaatctgg gcgtccccac cagtgcgggg	240
agccggaagg aggagccata gcttggagta ggtttggtt tggttgaaat aagaatttag	300
cctgtatgta ctgctttaac tcctggaaga	
atg aca gat gac aaa gat gtg	351
Met Thr Asp Asp Lys Asp Val	
1 5	
ctt cga gat gtg tgg ttt gga cga att cca act tgt ttc acg cta tat	399
Leu Arg Asp Val Trp Phe Gly Arg Ile Pro Thr Cys Phe Thr Leu Tyr	
8 13 18 23	
cag gat gag ata act gaa agg gaa gca gaa cca tac tat ttg ctt ttg	447
Gln Asp Glu Ile Thr Glu Arg Glu Ala Glu Pro Tyr Tyr Leu Leu Leu	
24 29 34 39	
cca aga gta agt tat ttg acg ttg gta act gac aaa gtg aaa aag cac	495
Pro Arg Val Ser Tyr Leu Thr Leu Val Thr Asp Lys Val Lys Lys His	
40 45 50 55	
ttt cag aag gtt atg aga caa gaa gac att agt gag ata tgg ttt gaa	543
Phe Gln Lys Val Met Arg Gln Glu Asp Ile Ser Glu Ile Trp Phe Glu	
56 61 66 71	
tat gaa ggc aca cca ctg aaa tgg cat tat cca att ggt ttg cta ttt	591
Tyr Glu Gly Thr Pro Leu Lys Trp His Tyr Pro Ile Gly Leu Leu Phe	
72 77 82 87	
gat ctt ctt gca tca agt tca gct ctt cct tgg aac atc aca gta cat	639
Asp Leu Leu Ala Ser Ser Ser Ala Leu Pro Trp Asn Ile Thr Val His	
88 93 98 103	
ttt aag agt ttt cca gaa aaa gac ctt ctg cac tgt cca tct aag gat	687
Phe Lys Ser Phe Pro Glu Lys Asp Leu Leu His Cys Pro Ser Lys Asp	
104 109 114 119	
gca att gaa gct cat ttt atg tca tgt atg aaa gaa gct gat gct tta	735

Ala Ile Glu Ala His Phe Met Ser Cys Met Lys Glu Ala Asp Ala Leu	
120 125 130 135	
aaa cat aaa agt caa gta atc aat gaa atg cag aaa aaa gat cac aag	783
Lys His Lys Ser Gln Val Ile Asn Glu Met Gln Lys Lys Asp His Lys	
136 141 146 151	
caa ctc tgg atg gga ttg caa aat gac aga ttt gac cag ttt tgg gcc	831
Gln Leu Trp Met Gly Leu Gln Asn Asp Arg Phe Asp Gln Phe Trp Ala	
152 157 162 167	
atc aat cgg aaa ctc atg gaa tat cct gca gaa gaa aat gga ttt cgt	879
Ile Asn Arg Lys Leu Met Glu Tyr Pro Ala Glu Glu Asn Gly Phe Arg	
168 173 178 183	
tat atc ccc ttt aga ata tat cag aca acg act gaa aga cct ttc att	927
Tyr Ile Pro Phe Arg Ile Tyr Gln Thr Thr Thr Glu Arg Pro Phe Ile	
184 189 194 199	
cag aag ctg ttt cgt cct gtg gct gca gat gga cag ttg cac aca cta	975
Gln Lys Leu Phe Arg Pro Val Ala Ala Asp Gly Gln Leu His Thr Leu	
200 205 210 215	
gga gat ctc ctc aaa gaa gtt tgt cct tct gct att gat cct gaa gat	1023
Gly Asp Leu Leu Lys Glu Val Cys Pro Ser Ala Ile Asp Pro Glu Asp	
216 221 226 231	
ggg gaa aaa aag aat caa gtg atg att cat gga att gag cca atg ttg	1071
Gly Glu Lys Lys Asn Gln Val Met Ile His Gly Ile Glu Pro Met Leu	
232 237 242 247	
gaa aca cct ctg cag tgg ctg agt gaa cat ctg agc tac ccg gat aat	1119
Glu Thr Pro Leu Gln Trp Leu Ser Glu His Leu Ser Tyr Pro Asp Asn	
248 253 258 263	
ttt ctt cat att agt atc atc cca cag cca aca gat tga aggatcaact	1168
Phe Leu His Ile Ser Ile Ile Pro Gln Pro Thr Asp *	
264 269 274	
atttgcctga acagaatcat ccttaaattgg gatttatcag agcatgtcac ccttttgctt	1228
caatcagggtt tgggtggaggc aacctgacca gaaacacttc gctgctgcaa gccagacagg	1288
aaaaagattc catgtcagat aaggcaactg ggctgggtctt actttgcatc acctctgctt	1348
tcctccactg ccatcattaa acctcagctg tgacatgaaa gacttaccgg accactgaag	1408
gtctttctgta aaatataatg aagctgaaac ctttggccta agaagaaaat ggaagtatgt	1468
gccactcgat ttgtatttct gattaacaaa taaacagggg tatttcctaa ggtgaccatg	1528
gttgaacttt agctcatgaa agtggaacaa ttggtttaatt tttcaagaga attaagaaag	1588
taaaagagaa attctgttat caataacttg caagtaattt tttgtaaaag attgaattac	1648
agtaaacccta tcttttcctta acgaaaattt cctatgttta cagtctgtct attgggtatgc	1708

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aatcttgtaa ctttgataat gaacagtgag agatTTTTta ataaagcctc taaatatggt 1768
ttgtcattta ataacataca gttttgtcac ttttcaagta ctttctgact cacatacagt 1828
agatcacttt ttactctgtg ttaccatttt gactggtcgt cattggcatg ggggtggatat 1888
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cctgtgttct ttacacacta cacgtataaa tattgtaact gttcatcttt gttgttttat 2008
cactgtaagc ctgtcaaadc atagtatcct aagcatctgt aaatgcta at tttgcatttt 2068
tgaaaaaacc cattccttcc aagctagtgt ttttcattgg ctccaggtct aattttttcac 2128
tgtggtcctt ggcagccagt cttttgaagt ttaaagatta cctgtctctt gactgcagta 2188
ccttttcttt aatttttacc aaaaatatcc agaggttact ggagttctta ttcaatataa 2248
ggaaagtttg ctgcacttta ttaccaagcc tctgggattt taccagtcaa acatatttgt 2308
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tgcttccttt tctttttcct tttgctgatt tcaactgatta atagcacatt tcttcacaaa 2548
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cattgccccat ttttacttcc tcattcatta ttgtaccagc atcatagctt tattactcta 3088
atcccaggta agtcaagcct acaatgccct agaggaagag taaaaccaga aattcatgct 3148
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aaaaattaaa taaaaaaaaa aaa 3231

```

<210> 156  
<211> 1073

<212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (337)..(720)

<400> 156

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ctctttttttt gggcacagca tccggctttt atttactaac tttgagaaca gagtaccttg      120
atcaattaaa tggtagggag cgctgtggag acagcatcct cccagtcctg ggaagagagg      180
cctaggatgc ctggggccca gcggcctctt ccctcctggc gtccccggct gccctcgctc      240
ccaggccccg cagtctcatt tgccgcttcc gacgcgtgac cccggcgcgc tagcgtccgg      300
gaccggtgac aggcgcgggg tgccccaagc agtccc  atg tgt ccc ctc cct ctc      354
                                         Met Cys Pro Leu Pro Leu
                                         1
```

```
gca gcc gcc gca gtc gct gcg ccc cga gcc cct ctc cgg ctc ctc aac      402
Ala Ala Ala Ala Val Ala Ala Pro Arg Ala Pro Leu Arg Leu Leu Asn
   7                12                17                22
```

```
aga ggg ctc gcc gcc gcc atg tct acc gcc cag tca ctc aaa tcc gtg      450
Arg Gly Leu Ala Ala Ala Met Ser Thr Ala Gln Ser Leu Lys Ser Val
  23                28                33                38
```

```
gac tac gag gtg ttc gga aga gtg cag ggt gtt tgc ttc aga atg tat      498
Asp Tyr Glu Val Phe Gly Arg Val Gln Gly Val Cys Phe Arg Met Tyr
  39                44                49                54
```

```
aca gaa gat gaa gct agg aaa ata gga gtg gtt ggc tgg gtg aag aat      546
Thr Glu Asp Glu Ala Arg Lys Ile Gly Val Val Gly Trp Val Lys Asn
  55                60                65                70
```

```
acc agc aaa ggc acc gtg aca ggc caa gtg cag ggg cca gaa gac aaa      594
Thr Ser Lys Gly Thr Val Thr Gly Gln Val Gln Gly Pro Glu Asp Lys
  71                76                81                86
```

```
gtc aat tcc atg aag tcc tgg ctg agc aag gtt gga agc cct agt tct      642
Val Asn Ser Met Lys Ser Trp Leu Ser Lys Val Gly Ser Pro Ser Ser
  87                92                97                102
```

```
cgc att gac cgc aca aac ttt tct aat gaa aaa acc atc tct aag ctt      690
Arg Ile Asp Arg Thr Asn Phe Ser Asn Glu Lys Thr Ile Ser Lys Leu
 103                108                113                118
```

```
gaa tac tct aat ttt agt att aga tac taa t agaagagaaa aattgtaaca      741
Glu Tyr Ser Asn Phe Ser Ile Arg Tyr  *
 119                124
```

```
cactgaacaa tagatactgt atgttcttaa gactatgtat actagaataa tagtagcaga      801
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```
gtagggtgaa aaggaacttt ctgttctgaa agctaagcga ctgtacgtgc tactaaaaat      861
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001050 "0943960

gtctgacact gaaataatTT tactcaacta tgTTTTcaac aagcaaaaat atagtattct 921  
aagattaaaa tgTcattaca aaatatttag tGTgaacatt taattttaac ttgtctcatg 981  
gaatcttttaa tttcaatgaa cattacagca tatatatgtt atttgGcgag acatcaaata 1041  
aagttaacca tttaaaaatt aaaaaaaaaa aa 1073

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<212> DNA  
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<222> (218) .. (1078)

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gccctttggg gggTacaaac aagagttcag ttgctgtgaa ttctgccact gtgcccagct 180  
ctgaagcctc agctcttgcc aaacagaccc gagaccc atg tca gcc cca ctg gat 235  
Met Ser Ala Pro Leu Asp  
1

gcc gcc ctc cac gcc ctt cag gag gag cag gcc aga ctc aag atg agg 283  
Ala Ala Leu His Ala Leu Gln GlU GlU Gln Ala Arg Leu Lys Met Arg  
7 12 17 22

ctg tgg gac ctg cag cag ctg aga aag gag ctc ggg gac tcc ccc aaa 331  
Leu Trp Asp Leu Gln Gln Leu Arg Lys GlU Leu Gly Asp Ser Pro Lys  
23 28 33 38

gac aag gtc cca ttt tca gtg ccc aag atc ccc ctg gta ttc cga gga 379  
Asp Lys Val Pro Phe Ser Val Pro Lys Ile Pro Leu Val Phe Arg Gly  
39 44 49 54

cac acc cag cag gac ccg gaa gtg cct aag tct tta gtt tcc aat ttg 427  
His Thr Gln Gln Asp Pro GlU Val Pro Lys Ser Leu Val Ser Asn Leu  
55 60 65 70

cgg atc cac tgc cct ctg ctt gcg ggc tct gct ctg atc acc ttt gat 475  
Arg Ile His Cys Pro Leu Leu Ala Gly Ser Ala Leu Ile Thr Phe Asp  
71 76 81 86

gac ccc aaa gtg gct gag cag gtg ctg caa caa aag gag cac acg atc 523  
Asp Pro Lys Val Ala GlU Gln Val Leu Gln Gln Lys GlU His Thr Ile  
87 92 97 102

aac atg gag gag tgc cgg ctg cgg gtg cag gtc cag ccc ttg gag ctg 571

Asn Met Glu Glu Cys Arg Leu Arg Val Gln Val Gln Pro Leu Glu Leu	
103 108 113 118	
ccc atg gtc acc acc atc cag gtg tcc agc cag ttg agt ggc cgg agg	619
Pro Met Val Thr Thr Ile Gln Val Ser Ser Gln Leu Ser Gly Arg Arg	
119 124 129 134	
gtg ttg gtc act gga ttt cct gcc agc ctc agg ctg agt gag gag gag	667
Val Leu Val Thr Gly Phe Pro Ala Ser Leu Arg Leu Ser Glu Glu Glu	
135 140 145 150	
ctg ctg gac aag cta gag atc ttc ttt ggc aag act agg aac gga ggt	715
Leu Leu Asp Lys Leu Glu Ile Phe Phe Gly Lys Thr Arg Asn Gly Gly	
151 156 161 166	
ggc gat gtg gac gtt cgg gag cta ctg cca ggg agt gtc atg ctg ggg	763
Gly Asp Val Asp Val Arg Glu Leu Leu Pro Gly Ser Val Met Leu Gly	
167 172 177 182	
ttt gct agg gat gga gtg gct cag cgt ctg tgc caa atc ggc cag ttc	811
Phe Ala Arg Asp Gly Val Ala Gln Arg Leu Cys Gln Ile Gly Gln Phe	
183 188 193 198	
aca gtg cca ctg ggt ggg cag caa gtc cct ctg aga gtc tct ccg tat	859
Thr Val Pro Leu Gly Gly Gln Gln Val Pro Leu Arg Val Ser Pro Tyr	
199 204 209 214	
gtg aat ggg gag atc cag aag gct gag atc agg tcg cag cca gtt ccc	907
Val Asn Gly Glu Ile Gln Lys Ala Glu Ile Arg Ser Gln Pro Val Pro	
215 220 225 230	
cgc tcg gta ctg gtg ctc aac att cct gat atc ttg gat ggc ccg gag	955
Arg Ser Val Leu Val Leu Asn Ile Pro Asp Ile Leu Asp Gly Pro Glu	
231 236 241 246	
ctg cat gac gtc ctg gag atc cac ttc cag aag ccc acc cgc ggg ggc	1003
Leu His Asp Val Leu Glu Ile His Phe Gln Lys Pro Thr Arg Gly Gly	
247 252 257 262	
ggg gag gta gag gcc ctg aca gtc gta ccc caa gga cag cag ggc cta	1051
Gly Glu Val Glu Ala Leu Thr Val Val Pro Gln Gly Gln Gln Gly Leu	
263 268 273 278	
gca gtc ttc acc tct gag tca ggc tag gggcc tccccttctc atcctcccca	1103
Ala Val Phe Thr Ser Glu Ser Gly *	
279 284	
cccccccgcc aaggttctca cactggcctg ggcttggggtg cccatatagg aggtctgtat	1163
gttcaccaac agtgcagagg gggtcacacat tgcaaaacac tgcccagaac agtaaaaaga	1223
gcctgcatgc caaaaaaaaaa aaa	1246



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 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (45) .. (449)

<400> 158

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 Met Met Lys Cys  
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cca cag gct tta cta gct atc ttt tgg ctt cta ctg agc tgg gtg agc 104  
 Pro Gln Ala Leu Leu Ala Ile Phe Trp Leu Leu Leu Ser Trp Val Ser  
 5 10 15 20

agt gaa gac aag gtg gta caa agc cct cta tct ctg gtt gtc cac gag 152  
 Ser Glu Asp Lys Val Val Gln Ser Pro Leu Ser Leu Val Val His Glu  
 21 26 31 36

gga gac acc gta act ctc aat tgc agt tat gaa gtg act aac ttt cga 200  
 Gly Asp Thr Val Thr Leu Asn Cys Ser Tyr Glu Val Thr Asn Phe Arg  
 37 42 47 52

agc cta cta tgg tac aag cag gaa aag aaa gct ccc aca ttt cta ttt 248  
 Ser Leu Leu Trp Tyr Lys Gln Glu Lys Lys Ala Pro Thr Phe Leu Phe  
 53 58 63 68

atg cta act tca agt gga att gaa aag aag tca gga aga cta agt agc 296  
 Met Leu Thr Ser Ser Gly Ile Glu Lys Lys Ser Gly Arg Leu Ser Ser  
 69 74 79 84

ata tta gat aag aaa gaa ctt tcc agc atc ctg aac atc aca gcc acc 344  
 Ile Leu Asp Lys Lys Glu Leu Ser Ser Ile Leu Asn Ile Thr Ala Thr  
 85 90 95 100

cag acc gga gac tcg gcc atc tac ctc tgt gct gtg gag gca cag tgc 392  
 Gln Thr Gly Asp Ser Ala Ile Tyr Leu Cys Ala Val Glu Ala Gln Cys  
 101 106 111 116

tcc cta gtc acc tgc agc ctg tac tca aat tct aca gct gag gct ctg 440  
 Ser Leu Val Thr Cys Ser Leu Tyr Ser Asn Ser Thr Ala Glu Ala Leu  
 117 122 127 132

caa ctg taa gatgggg aacttgctac attgagcaag ccctcaaaaa taaactatac 496  
 Gln Leu \*  
 133

ggaaaagcag ttattggtca aaaaaaaaaa aaaa 530

<210> 159  
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 <212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (94)..(1341)

<400> 159

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agactcttag ctgaacgcgg agctgcggcg gct atg ctg tgg agc ggc tgc cgg 114  
Met Leu Trp Ser Gly Cys Arg  
1 5

cgt ttc ggg gcg cgc ctc ggc tgc ctg ccc ggc ggt ctc cgg gtc ctc 162  
Arg Phe Gly Ala Arg Leu Gly Cys Leu Pro Gly Gly Leu Arg Val Leu  
8 13 18 23

gtc cag acc ggc cac cgg agc ttg acc tcc tgc atc gac cct tcc atg 210  
Val Gln Thr Gly His Arg Ser Leu Thr Ser Cys Ile Asp Pro Ser Met  
24 29 34 39

gga ctt aat gaa gag cag aaa gaa ttt caa aaa gtg gcc ttt gac ttt 258  
Gly Leu Asn Glu Glu Gln Lys Glu Phe Gln Lys Val Ala Phe Asp Phe  
40 45 50 55

gct gcc cga gag atg gct cca aat atg gca gag tgg gac cag aag gag 306  
Ala Ala Arg Glu Met Ala Pro Asn Met Ala Glu Trp Asp Gln Lys Glu  
56 61 66 71

ctg ttc cca gtg gat gtg atg cgg aag gca gcc cag cta ggc ttc gga 354  
Leu Phe Pro Val Asp Val Met Arg Lys Ala Ala Gln Leu Gly Phe Gly  
72 77 82 87

ggg gtc tac ata caa aca gat gtg ggc ggg tct ggg ctg tca cgt ctt 402  
Gly Val Tyr Ile Gln Thr Asp Val Gly Gly Ser Gly Leu Ser Arg Leu  
88 93 98 103

gat acc tct gtc att ttt gaa gcc ttg gct aca ggc tgc acc agc acc 450  
Asp Thr Ser Val Ile Phe Glu Ala Leu Ala Thr Gly Cys Thr Ser Thr  
104 109 114 119

aca gcc tat ata agc atc cac aac atg tgt gcc tgg atg att gat agc 498  
Thr Ala Tyr Ile Ser Ile His Asn Met Cys Ala Trp Met Ile Asp Ser  
120 125 130 135

ttc gga aat gag gaa cag agg cac aaa ttt tgc cca ccg ctc tgt acc 546  
Phe Gly Asn Glu Glu Gln Arg His Lys Phe Cys Pro Pro Leu Cys Thr  
136 141 146 151

atg gag aag ttt gct tcc tac tgc ctc act gaa cca gga agt ggg agt 594  
Met Glu Lys Phe Ala Ser Tyr Cys Leu Thr Glu Pro Gly Ser Gly Ser  
152 157 162 167

gat gct gcc tct ctt ctg acc tcc gct aag aaa cag gga gat cat tac 642  
Asp Ala Ala Ser Leu Leu Thr Ser Ala Lys Lys Gln Gly Asp His Tyr  
168 173 178 183



Ile Ser Arg Ser Leu Leu Gln Glu \*

408

413

ttcagtgcga ctgcagtcag tggtgagtg tgccatgtgg gccgctctat tccaaaggaa 1426  
 tcatggatta gacccaaggg ctgagctcct ctagggcagg acctgcaccc tgtgtgttg 1486  
 caccagcatc gggctcttga ctggggcaga atccccagtg gaaccggaag agctggactg 1546  
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 aatattttta atcacattga taaaatctat ccttcaccac ctctggttct actatagttg 2146  
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 cgccaggcag tggccccgcc atg tcc cag ccc cgg acc cca gag cag gca 170  
 Met Ser Gln Pro Arg Thr Pro Glu Gln Ala  
 1 5  
 ctg gat aca ccg ggg gac tgc ccc cca ggc agg aga gac gag gac gct 218  
 Leu Asp Thr Pro Gly Asp Cys Pro Pro Gly Arg Arg Asp Glu Asp Ala  
 11 16 21 26





Ile 68	Ser	Asp	Leu	Leu	Met 73	Ile	Leu	Thr	Phe	Pro 78	Phe	Lys	Ile	Leu	Ser 83	
gat 84	gcc	aaa	ctg	gga	aca 89	gga	cca	ctg	aga	act 94	ttt	gtg	tgt	caa	gtt 99	585
Asp	Ala	Lys	Leu	Gly	Thr	Gly	Pro	Leu	Arg	Thr	Phe	Val	Cys	Gln	Val	
acc 100	tcc	gtc	ata	ttt	tat 105	ttc	aca	atg	tat	atc 110	agt	att	tca	ttc	ctg 115	633
Thr	Ser	Val	Ile	Phe	Tyr	Phe	Thr	Met	Tyr	Ile	Ser	Ile	Ser	Phe	Leu	
gga 116	ctg	ata	act	atc	gat 121	cgc	tac	cag	aag	acc 126	acc	agg	cca	ttt	aaa 131	681
Gly	Leu	Ile	Thr	Ile	Asp	Arg	Tyr	Gln	Lys	Thr	Thr	Arg	Pro	Phe	Lys	
aca 132	tcc	aac	ccc	aaa	aat 137	ctc	ttg	ggg	gct	aag 142	att	ctc	tct	gtt	gtc 147	729
Thr	Ser	Asn	Pro	Lys	Asn	Leu	Leu	Gly	Ala	Lys	Ile	Leu	Ser	Val	Val	
atc 148	tgg	gca	ttc	atg	ttc 153	tta	ctc	tct	ttg	cct 158	aac	atg	att	ctg	acc 163	777
Ile	Trp	Ala	Phe	Met	Phe	Leu	Leu	Ser	Leu	Pro	Asn	Met	Ile	Leu	Thr	
aac 164	agg	cag	ccg	aga	gac 169	aag	aat	gtg	aag	aaa 174	tgc	tct	ttc	ctt	aaa 179	825
Asn	Arg	Gln	Pro	Arg	Asp	Lys	Asn	Val	Lys	Lys	Cys	Ser	Phe	Leu	Lys	
tca 180	gag	ttc	ggt	cta	gtc 185	tgg	cat	gaa	ata	gta 190	aat	tac	atc	tgt	caa 195	873
Ser	Glu	Phe	Gly	Leu	Val	Trp	His	Glu	Ile	Val	Asn	Tyr	Ile	Cys	Gln	
gtc 196	att	ttc	tgg	att	aat 201	ttc	tta	att	gtt	att 206	gta	tgt	tat	aca	ctc 211	921
Val	Ile	Phe	Trp	Ile	Asn	Phe	Leu	Ile	Val	Ile	Val	Cys	Tyr	Thr	Leu	
att 212	aca	aaa	gaa	ctg	tac 217	cgg	tca	tac	gta	aga 222	acg	agg	ggt	gta	ggt 227	969
Ile	Thr	Lys	Glu	Leu	Tyr	Arg	Ser	Tyr	Val	Arg	Thr	Arg	Gly	Val	Gly	
aaa 228	gtc	ccc	agg	aaa	aag 233	gtg	aac	gtc	aaa	gtt 238	ttc	att	atc	att	gct 243	1017
Lys	Val	Pro	Arg	Lys	Lys	Val	Asn	Val	Lys	Val	Phe	Ile	Ile	Ile	Ala	
gta 244	ttc	ttt	att	tgt	ttt 249	gtt	cct	ttc	cat	ttt 254	gcc	cga	att	cct	tac 259	1065
Val	Phe	Phe	Ile	Cys	Phe	Val	Pro	Phe	His	Phe	Ala	Arg	Ile	Pro	Tyr	
acc 260	ctg	agc	caa	acc	cgg 265	gat	gtc	ttt	gac	tgc 270	act	gct	gaa	aat	act 275	1113
Thr	Leu	Ser	Gln	Thr	Arg	Asp	Val	Phe	Asp	Cys	Thr	Ala	Glu	Asn	Thr	
ctg 276	ttc	tat	gtg	aaa	gag 281	agc	act	ctg	tgg	tta 286	act	tcc	tta	aat	gca 291	1161
Leu	Phe	Tyr	Val	Lys	Glu	Ser	Thr	Leu	Trp	Leu	Thr	Ser	Leu	Asn	Ala	
tgc 1209	ctg	gat	ccg	ttc	atc	tat	ttt	ttc	ctt	tgc	aag	tcc	ttc	aga	aat	
Cys	Leu	Asp	Pro	Phe	Ile	Tyr	Phe	Phe	Leu	Cys	Lys	Ser	Phe	Arg	Asn	

292	297	302	307	
tcc ttg ata agt atg ctg aag tgc ccc aat tct gca aca tct ctg tcc				1257
Ser Leu Ile Ser Met Leu Lys Cys Pro Asn Ser Ala Thr Ser Leu Ser				
308	313	318	323	
cag gac aat agg aaa aaa gaa cag gat ggt ggt gac cca aat gaa gag				1305
Gln Asp Asn Arg Lys Lys Glu Gln Asp Gly Gly Asp Pro Asn Glu Glu				
324	329	334	339	
act cca atg taa aca aattaactaa ggaaatatatt caatctcttt gtgttcagaa				1360
Thr Pro Met *				
340				
ctcgttaaag caaagcgcta agtaaaaata ttaactgacg aagaagcaac taagttaata				1420
ataatgactc taaagaaaca gaagattaca aaagcaattt tcatttacct ttccagtatg				1480
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caaaaaatga tagntaaaat gtatataata tctagtcccc taacccaaat ncttgaccta				1780
ttgggatact taataaaaaa ttaaagtaag tgggataccc caaagaaata ataactattt				1840
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Met Val His Leu Thr Pro Glu Glu Lys Ser Ala Val Thr				
1 5 10				
gcc ctg tgg ggc aag gtg aac gtg gat gaa gtt ggt ggt gag gcc ctg				158



Ala	Leu	Trp	Gly	Lys	Val	Asn	Val	Asp	Glu	Val	Gly	Gly	Glu	Ala	Leu		
14					19					24					29		
ggc	agg	ctg	ctg	gtg	gtc	tac	cct	tgg	acc	cag	agg	ttc	ttt	gag	tcc		206
Gly	Arg	Leu	Leu	Val	Val	Tyr	Pro	Trp	Thr	Gln	Arg	Phe	Phe	Glu	Ser		
30					35					40					45		
ttt	ggg	gat	ctg	tcc	act	cct	gat	gct	gtt	atg	ggc	aac	cct	aag	gtg		254
Phe	Gly	Asp	Leu	Ser	Thr	Pro	Asp	Ala	Val	Met	Gly	Asn	Pro	Lys	Val		
46					51					56					61		
aag	gct	cat	ggc	aag	aaa	gtg	ctc	ggt	gcc	ttt	agt	gat	ggc	ctg	gct		302
Lys	Ala	His	Gly	Lys	Lys	Val	Leu	Gly	Ala	Phe	Ser	Asp	Gly	Leu	Ala		
62					67					72					77		
cac	ctg	gac	aac	ctc	aag	ggc	acc	ttt	gcc	aca	ctg	agt	gag	ctg	cac		350
His	Leu	Asp	Asn	Leu	Lys	Gly	Thr	Phe	Ala	Thr	Leu	Ser	Glu	Leu	His		
78					83					88					93		
tgt	gac	aag	ctg	cac	gtg	gat	cct	gag	aac	ttc	agg	ctc	ctg	ggc	aac		398
Cys	Asp	Lys	Leu	His	Val	Asp	Pro	Glu	Asn	Phe	Arg	Leu	Leu	Gly	Asn		
94					99					104					109		
gtg	ctg	gtc	tgt	gtg	ctg	gcc	cat	cac	ttt	ggc	aaa	gaa	ttc	acc	cca		446
Val	Leu	Val	Cys	Val	Leu	Ala	His	His	Phe	Gly	Lys	Glu	Phe	Thr	Pro		
110					115					120					125		
cca	gtt	gca	ggc	ttg	cct	atc	aga	aag	ttg	gtg	gct	ggt	tgt	ggc	taa		494
Pro	Val	Ala	Gly	Leu	Pro	Ile	Arg	Lys	Leu	Val	Ala	Gly	Cys	Gly	*		
126					131					136					141		
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aggtaaactc	ccctctttga	cttctggcca	gggtttgtgc	tgagctggct	gcagccgctc												240



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Gln Gly Leu Val Ser Lys Ala Gly Trp Leu Ile Gly Tyr Ile Leu Ile	
210 215 220 225	
aca gaa ttt gtt ggg cgg aga tat cgg aga aca gtg ggg att ttt tac	1017
Thr Glu Phe Val Gly Arg Arg Tyr Arg Arg Thr Val Gly Ile Phe Tyr	
226 231 236 241	
caa gtt gcc tat aca gtt ggg ctc ctg gtg cta gct ggg gtg gct tac	1065
Gln Val Ala Tyr Thr Val Gly Leu Leu Val Leu Ala Gly Val Ala Tyr	
242 247 252 257	
gca ctt cct cac tgg agg tgg ttg cag ttc aca gtt gct ctg ccc aac	1113
Ala Leu Pro His Trp Arg Trp Leu Gln Phe Thr Val Ala Leu Pro Asn	
258 263 268 273	
ttc ttc ttc ttg ctc tat tac tgg tgc ata cct gag tct ccc agg tgg	1161
Phe Phe Phe Leu Leu Tyr Tyr Trp Cys Ile Pro Glu Ser Pro Arg Trp	
274 279 284 289	
ctg atc tcc cag aat aag aat gct gaa gcc atg aga atc att aag cac	1209
Leu Ile Ser Gln Asn Lys Asn Ala Glu Ala Met Arg Ile Ile Lys His	
290 295 300 305	
atc gca aag aaa aat gga aaa tct cta ccc gcc tcc ctt cag cgc ctg	1257
Ile Ala Lys Lys Asn Gly Lys Ser Leu Pro Ala Ser Leu Gln Arg Leu	
306 311 316 321	
aga ctt gaa gag gaa act ggc aag aaa ttg aac cct tca ttt ctt gac	1305
Arg Leu Glu Glu Glu Thr Gly Lys Lys Leu Asn Pro Ser Phe Leu Asp	
322 327 332 337	
ttg gtc aga act cct cag ata agg aaa cat act atg ata ttg atg tac	1353
Leu Val Arg Thr Pro Gln Ile Arg Lys His Thr Met Ile Leu Met Tyr	
338 343 348 353	
aac tgg ttc acg agc tct gtg ctc tac cag ggc ctc atc atg cac atg	1401
Asn Trp Phe Thr Ser Ser Val Leu Tyr Gln Gly Leu Ile Met His Met	
354 359 364 369	
ggc ctt gca ggt gac aat atc tac ctg gat ttc ttc tac tct gcc ctg	1449
Gly Leu Ala Gly Asp Asn Ile Tyr Leu Asp Phe Phe Tyr Ser Ala Leu	
370 375 380 385	
gtt gaa ttc cca gct gcc ttc atg atc atc ctc acc atc gac cgc atc	1497
Val Glu Phe Pro Ala Ala Phe Met Ile Ile Leu Thr Ile Asp Arg Ile	
386 391 396 401	
gga cgc cgt tac cct tgg gct gca tca aat atg gtt gca ggg gca gcc	1545
Gly Arg Arg Tyr Pro Trp Ala Ala Ser Asn Met Val Ala Gly Ala Ala	
402 407 412 417	
tgt ctg gcc tca gtt ttt ata cct ggt gat cta caa tgg cta aaa att	1593
Cys Leu Ala Ser Val Phe Ile Pro Gly Asp Leu Gln Trp Leu Lys Ile	
418 423 428 433	
att atc tca tgc ttg gga aga atg ggg atc aca atg gcc tat gag ata	1641

Ile	Ile	Ser	Cys	Leu	Gly	Arg	Met	Gly	Ile	Thr	Met	Ala	Tyr	Glu	Ile					
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Val	Cys	Leu	Val	Asn	Ala	Glu	Leu	Tyr	Pro	Thr	Phe	Ile	Arg	Asn	Leu					
450					455					460					465					
ggc	gtc	cac	atc	tgt	tcc	tca	atg	tgt	gac	att	ggg	ggc	atc	atc	acg	1737				
Gly	Val	His	Ile	Cys	Ser	Ser	Met	Cys	Asp	Ile	Gly	Gly	Ile	Ile	Thr					
466					471					476					481					
cca	ttc	ctg	gtc	tac	cgg	ctc	act	aac	atc	tgg	ctt	gag	ctc	ccg	ctg	1785				
Pro	Phe	Leu	Val	Tyr	Arg	Leu	Thr	Asn	Ile	Trp	Leu	Glu	Leu	Pro	Leu					
482					487					492					497					
atg	gtt	ttc	ggc	gta	ctt	ggc	ttg	gtt	gct	gga	ggg	ctg	gtg	ctg	ttg	1833				
Met	Val	Phe	Gly	Val	Leu	Gly	Leu	Val	Ala	Gly	Gly	Leu	Val	Leu	Leu					
498					503					508					513					
ctt	cca	gaa	act	aaa	ggg	aaa	gct	ttg	cct	gag	acc	atc	gag	gaa	gcc	1881				
Leu	Pro	Glu	Thr	Lys	Gly	Lys	Ala	Leu	Pro	Glu	Thr	Ile	Glu	Glu	Ala					
514					519					524					529					
gaa	aat	atg	caa	aga	cca	aga	aaa	aat	aaa	gaa	aag	atg	att	tac	ctc	1929				
Glu	Asn	Met	Gln	Arg	Pro	Arg	Lys	Asn	Lys	Glu	Lys	Met	Ile	Tyr	Leu					
530					535					540					545					
caa	gtt	cag	aaa	cta	gac	att	cca	ttg	aac	taa	gaagagag accgttgctg				1980					
Gln	Val	Gln	Lys	Leu	Asp	Ile	Pro	Leu	Asn	*										
546					551					556										
ctgtcatgac ctagctttga tggcagcaag accaaaagta gaaatccctg cactcatcac																2040				
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<222> (69)..(917)

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<221> misc\_feature

<222> (1)...(2029)

<223> n = a,t,c or g

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Met Leu Gly Val Asn Pro Arg Phe Asp Ser Ala Ser Ser Ser  
1 5 10

tac tat ttg gac atg cac agc ctc ccc cat gtc atc aac cca gtg gag 158  
Tyr Tyr Leu Asp Met His Ser Leu Pro His Val Ile Asn Pro Val Glu  
15 20 25 30

tcc cgg ctg gga tcc agt gct gcc tcc ttg tac cct gtg ctc aac ttt 206  
Ser Arg Leu Gly Ser Ser Ala Ala Ser Leu Tyr Pro Val Leu Asn Phe  
31 36 41 46

cta ctc tac gtg cct gag ctt gca cac tca ccg ctg tac att cag gac 254  
Leu Leu Tyr Val Pro Glu Leu Ala His Ser Pro Leu Tyr Ile Gln Asp  
47 52 57 62

aag gat ggc gct cca gtg gcc acc aat gcc ttc cat agt ccc cgc tgg 302  
Lys Asp Gly Ala Pro Val Ala Thr Asn Ala Phe His Ser Pro Arg Trp  
63 68 73 78

ggg ggc att atg gta tat aat gtt gac tcc aaa acc tat aat gcc tca 350  
Gly Gly Ile Met Val Tyr Asn Val Asp Ser Lys Thr Tyr Asn Ala Ser  
79 84 89 94

gtg ctg cca gtg aga gtc gag gtg gac atg gtg cga gtg atg gag gtg 398  
Val Leu Pro Val Arg Val Glu Val Asp Met Val Arg Val Met Glu Val  
95 100 105 110

ttc ctg gca cag ttg cgg ttg ctc ttt ggg att gct cag ccc cag ctg 446  
Phe Leu Ala Gln Leu Arg Leu Leu Phe Gly Ile Ala Gln Pro Gln Leu  
111 116 121 126

cct cca aaa tgc ctg ctt tca ggg cct acg agt gaa ggg cta atg acc 494  
Pro Pro Lys Cys Leu Leu Ser Gly Pro Thr Ser Glu Gly Leu Met Thr  
127 132 137 142

tgg gag cta gac cgg ctg ctc tgg gct cgg tca gtg gag aac ctg gcc 542  
Trp Glu Leu Asp Arg Leu Leu Trp Ala Arg Ser Val Glu Asn Leu Ala  
143 148 153 158

aca gcc acc acc acc ctt acc tcc ctg gcg cag ctt ctg ggc aag atc 590  
Thr Ala Thr Thr Thr Leu Thr Ser Leu Ala Gln Leu Leu Gly Lys Ile  
159 164 169 174

agc aac att gtc att aag gac gac gtg gca tct gag gtg tac aag gct 638  
Ser Asn Ile Val Ile Lys Asp Asp Val Ala Ser Glu Val Tyr Lys Ala  
175 180 185 190



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gaagctgtga catcctcacg aaatcgtcga cccgggaatt ccggnccggt cctgcaggcg 2007  
acaggcttac aatggcgagc ct 2029